

The American Journal of Medicine

Editor ALEXANDER B. GUTMAN, M. D.

Professor of Medicine, COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK

ADVISORY BOARD

Chairman: WALTER W. PALMER, M.D., Bard Professor Emeritus, Columbia University College of Physicians and Surgeons, New York; DAVID P. BARR, M.D., Professor of Medicine, Cornell University Medical College, New York; ARTHUR L. BLOOMFIELD, M.D., Professor of Medicine, School of Medicine, Stanford University, San Francisco; FRANCIS G. BLAKE, M.D., Sterling Professor of Medicine, Yale University School of Medicine, New Haven; EUGENE A. STEAD, JR., M.D., Professor of Medicine, School of Medicine, Duke University, Durham; JOSEPH T. WEARN, M.D., Professor of Medicine, School of Medicine, Western Reserve University, Cleveland.

ASSOCIATE EDITORS

HERRMAN L. BLUMGART, M.D., *Boston*; HARRY GOLD, M.D., *New York*; A. MCGEE HARVEY, M.D., *Baltimore*; GEORGE H. HOUCK, M.D., *San Francisco*; CHESTER S. KEEFER, M.D., *Boston*; T. GRIER MILLER, M.D., *Philadelphia*; WALTER L. PALMER, M.D., *Chicago*; OSWALD H. ROBERTSON, M.D., *Chicago*; EPHRAIM SHORR, M.D., *New York*; GEORGE W. THORN, M.D., *Boston*; WILLIAM S. TILLET, M.D., *New York*; ROY H. TURNER, M.D., *New Orleans*; RUSSELL M. WILDER, M.D., *Rochester*; M. M. WINTROBE, M.D., *Salt Lake City*; W. BARRY WOOD, M.D., *St. Louis*; JOHN B. YOUNG, M.D., *Chicago*.

Volume VII

JULY TO DECEMBER

1949

THE YORKE PUBLISHING COMPANY, INC.

NEW YORK

MCMXLIX

CONTENTS OF VOLUME VII

ORIGINAL ARTICLES

Retro-spect and Pro-spect, 1949	<i>Alexander B. Gutman</i>	1
Clinical Manifestations of Intercapillary Glomerulosele- rosis in Diabetes Mellitus	<i>{ George V. Mann Carl Gardner Howard F. Root</i>	3
Experiences with the Kolff Artificial Kidney	<i>{ Alfred P. Fishman Irving G. Kroop H. Evans Leiter Abraham Hyman</i>	15
Transperitoneal Lavage for Twenty-six Days in the Treat- ment of Azotemia	<i>{ G. K. Fenn L. A. Nalefski J. Lasner</i>	35
Acute Urinary Suppression. Observations in Twenty-two Patients	<i>Richard J. Stock</i>	45
Clinical and Metabolic Study of 11-Dehydro-17-hydroxy- corticosterone Acetate (Kendall Compound E) in Hypertension, Addison's Disease and Diabetes Mellitus	<i>{ George A. Perera Kermit L. Pines Howard B. Hamilton Katherine Vistocky</i>	56
Role of the Neurohypophysis in the Pathogenesis of Hy- pertension and Some Allied Disorders Associated with Aging	<i>Thomas Findley</i>	70
Origin and Nature of Antibiotics	<i>Selman A. Waksman</i>	85
The Adrenal Cortex		100
Progressive Hepatic Disease		114
American Federation for Clinical Research- Abstracts of Papers Presented at the Southern Sectional Meeting Held in New Orleans, January 28, 1949		126
Chronic Pancreatitis	<i>Russell D. Williams</i>	137
Mezaioblastic Bone Marrow in Liver Disease	<i>E. R. Moritt</i>	145
Epileptic Equivalents, A Cause for Somatic Symptoms	<i>H. M. Winans</i>	150
Vagotomy for Peptic Ulcer	<i>T. Grier Miller</i>	153
Intubation Studies in Intestinal Allergy	<i>Eugene M. Schloss</i>	156
i Mordity of the Human Esophagus in Control Subjects and in Patients with Esophageal Disorders	<i>{ Philip Kramer Franz J. Ingelfinger</i>	168
ii Cardiospasm, A Generalized Disorder of Esophageal Mordity	<i>{ Philip Kramer Franz J. Ingelfinger</i>	174

A Unified Concept of Cardiac Failure.	<i>J. Maxwell Little</i>	207
Dosage Forms of Penicillin for Systemic Infections	<i>Chester S. Keefer</i>	216
Psychogenic Deafness in a Disturbed Boy.	221
Cardiac Failure, Elevated Basal Metabolic Rate and Psychosis	228
Southern Society for Clinical Research—Abstracts of Papers Presented at the Third Annual Meeting Held in New Orleans, January 29, 1949	241
Thyrotoxicosis Simulating Hyperparathyroidism.	<i>Malcolm M. Stanley</i> <i>Joseph Fazekas</i>	262
Influenzal Meningitis in Adults. Report of a Case Complicating the Nephrotic Syndrome	<i>Marvin C. Becker</i> <i>Clifford L. Spingarn</i>	269
Endocarditis Due to <i>Hemophilus Influenzae</i>	<i>Frederick C. Goetz</i> <i>Edwin W. Peterson</i>	274
Multiple Pulmonary Artery Aneurysms. Endarteritis of Ductus Arteriosus and Congenital Pulmonary Cysts	<i>Marvin Lillian</i>	280
Relapsing Febrile Non-suppurative Panniculitis. (Weber-Christian Disease).	<i>Samuel H. Rubin</i> <i>John H. Bland</i>	288
Disinfection of the Air with Triethylene Glycol Vapor	<i>O. H. Robertson</i>	293
I. Electrophoretic, Nitrogen and Lipide Analyses of Plasma and Plasma Fractions of Healthy Young Men	<i>H. Rowland Pearsall</i> <i>Alfred Chanutin</i>	297
II. Electrophoretic, Nitrogen and Lipide Analyses of Plasma and Plasma Fractions in Disease	<i>H. Rowland Pearsall</i> <i>Alfred Chanutin</i>	301
A Spontaneously Precipitable Protein in Human Sera, with Particular Reference to the Diagnosis of Polyarteritis Nodosa	<i>Harold Lepow</i> <i>Leo Rubenstein</i> <i>Fanya Woll</i> <i>Harry Greisman</i>	310
Acute Diffuse Glomerulonephritis	<i>Jan Brod</i>	317
Pulmonary Adenomatosis	<i>Sylvia Bubis</i> <i>James H. Erwin</i>	336
Chronic Pulmonary Granulomatosis. Report of Ten Cases	<i>J. M. DeNardi</i> <i>H. S. Van Ordstrand</i> <i>M. G. Carmody</i> <i>F. Tremaine Billings, Jr.</i> <i>Bernard M. Kalstone</i>	345
—Prognosis of Acute Myocardial Infarction.	<i>James L. Spencer</i> <i>Con O. T. Ball</i> <i>George R. Meneely</i> <i>Ralph Tompsett</i> <i>Walsh McDermott</i>	356
Recent Advances in Streptomycin Therapy	371
Acute Diffuse Glomerulonephritis	382
Chronic Pleurisy and Peritonitis	396
American Federation for Clinical Research. Abstracts of Papers Presented at the National Meeting Held in Atlantic City, May 3, 1949	407
Diffuse Progressive Interstitial Fibrosis of the Lungs.	<i>A. J. Beams</i> <i>O. Harnos</i>	425

A Syndrome Characterized by Generalized Cutaneous Eruption, Chorioretinitis and Eosinophilia, Probably Due to Chronic Toxoplasma Infection	{ <i>Andrew J. Brennan</i> <i>Thomas McP. Brown</i> <i>Joel Warren</i> <i>George Vranian</i>	431
Treatment of Auricular Flutter with Digitalis	<i>Arthur L. Bloomfield</i>	437
Some Effects of Digoxin upon the Heart and Circulation in Man. Digoxin in Left Ventricular Failure	{ <i>Réjane M. Harvey</i> <i>M. Irené Ferrer</i> <i>Richard T. Cathcart</i> <i>Dickinson W. Richards, Jr.</i> <i>André Cournand</i>	439
Coarctation of the Aorta. Photo-electric Plethysmography and Direct Arterial Blood Pressure Measurement as an Aid in Diagnosis	{ <i>Melvin L. Goldman</i> <i>Henry A. Schroeder</i>	454
Acute Coronary Insufficiency Due to Pulmonary Embolism	{ <i>Simon Dack</i> <i>Arthur M. Master</i> <i>Henry Horn</i> <i>Arthur Grishman</i> <i>Leonard E. Field</i>	464
Auricular Fibrillation without Other Evidence of Heart Disease. A Cause of Reversible Heart Failure	{ <i>Edward Phillips</i> <i>Samuel A. Levine</i>	478
Function of the Kidney and Metabolic Changes in Cardiac Failure	<i>Elliot V. Newman</i>	490
Tricuspid Stenosis—A Simple Diagnostic Sign	<i>Harry Vesell</i>	497
Diaphragmatic Hiatus Hernia. With Severe Iron-deficient Anemia	{ <i>Steven O. Schwartz</i> <i>Sunoll A. Blumenthal</i>	501
Biologic Complications of Penicillin Therapy	{ <i>Leonard S. Sommer</i> <i>Cutting B. Favour</i>	511
Aureomycin in the Treatment of Tularemia	{ <i>John C. Ransmeier</i> <i>Harry J. Price</i> <i>Zerney B. Barnes, Jr.</i>	518
Newer Concepts of the Role of Potassium in Disease	<i>T. S. Danowski</i>	525
Aureomycin in the Treatment of Infectious Diseases	{ <i>Harry M. Rose</i> <i>Tale Kneeland, Jr.</i>	532
Pneumonia, Skin Eruption, Thrombophlebitis and Azotemia	542
Intestinal Lipodystrophy (Whipple's Disease)	{ <i>Paul J. Schutz</i> <i>William H. Benner</i> <i>William A. Christian</i>	553
Thrombocytopenic Purpura Complicating Radioactive Phosphorus Treatment in a Patient with Polycythemia Vera	<i>Gould A. Andrews</i>	564
Foreword	<i>Russell M. Wilder</i>	569
Carbohydrate Metabolism	<i>DeWitt Stetten, Jr.</i>	571
Studies in Experimental Diabetes	<i>R. E. Haist</i>	585
Association of Diabetes Mellitus and Disorders of the Anterior Pituitary, Thyroid and Adrenal Cortex	{ <i>William M. Balfour</i> <i>Randall G. Sprague</i>	596
Pregnancy Complicating Diabetes	<i>Priscilla White</i>	609

Arteriosclerosis and Diabetes	<i>Joseph H. Barach</i>	617
Management of Diabetes in a General Medical Practice.	<i>Russell M. Wilder, Jr.</i>	625
Diabetic Coma. Metabolic Derangements and Principles for Corrective Therapy	<i>George M. Guest</i>	630
Changes in the Volume of the Plasma, Interstitial and Intracellular Fluid Spaces During Hydration and Dehydration in Normal and Edematous Subjects.	<i>{ Samuel E. Leard Edward D. Freis }</i>	647
Insulin Mixtures. Experiences in the Use of Extemporaneous Bottle Mixtures in Diabetic Clinic Patients	<i>{ Bert H. Wiesel A. Bankston Riser Stanley S. Kahn }</i>	655
Cardiac Complications of Diabetes Mellitus	<i>{ Irving M. Liebow Herman K. Hellerstein }</i>	660
Chloramphenicol (Chloromycetin) in the Treatment of Infectious Diseases	<i>Joseph E. Smadel</i>	671
Tetanus Following Dental Extraction	<i>{ Dwight Griswold Albert C. Herring }</i>	686
Loeffler's Syndrome with Associated Eosinophilic Polyserositis	<i>{ Helen A. Dickie Elizabeth Grimm }</i>	690
Kala-azar. With Special Studies of Bone Marrow and Lymph Nodes	<i>{ William J. Senter Harold Sutker Hortense Elton Garver }</i>	694
Infectious Mononucleosis	<i>George H. Houck</i>	699
Radioiodotherapeusis	<i>{ Robert H. Williams Beverly T. Towery Herbert Jaffe Walter F. Rogers, Jr. Rene Tagnon }</i>	702
Factors Influencing the Effectiveness of Radioiodotherapeusis	<i>{ Robert H. Williams Herbert Jaffe Beverly T. Towery Walter F. Rogers, Jr. Rene Tagnon }</i>	718
Radioactive Iodine, I ¹³¹ , in the Treatment of Hyperthyroidism	<i>{ Sidney C. Werner Edith H. Quimby Charlotte Schmidt }</i>	731
Effect of Adrenocorticotrophic Hormone (ACTH) on Rheumatoid Arthritis.	<i>{ Charles Ragan Albert W. Grokoest Ralph H. Boots }</i>	741
Some Technics for Recording the Ballistocardiogram Directly from the Body	<i>{ William Dock Felix Taubman }</i>	751
Effects of Clockwise Rotation of the Heart on the Electrocardiogram.	<i>Emanuel Goldberger</i>	756
Electrocardiographic Evaluation of Boeck's Sarcoid and Advanced Pulmonary Tuberculosis. Special Reference to Interpretation of the Multiple Unipolar Leads	<i>Safety R. First</i>	760

Hemiplegia Attending Acute Myocardial Infarction . . .	{ William Bennett Bean . . . Gerald W. Flamm . . . Albert Sapadin . . . }	765
The Role of Allergy in the Pathogenesis of Rheumatic Fever	Edward E. Fischel . . .	772
Bacitracin	{ Frank L. Meleney . . . Balbina A. Johnson . . }	794
The Polymyxins. A Review and Assessment	Philip G. Stansly . . .	807
Anorexia Nervosa		819
Weakness, Weight Loss and Prostration		825
Coarctation of the Aorta	{ E. R. Hayes . . . H. M. Stauffer . . . }	835
Regional Enteritis Complicated by Pylephlebitis and Multiple Liver Abscesses	Frederic W. Taylor . . .	838
Hemophilia in Twins	{ Armand J. Quick . . . James P. Conway . . . }	841

COPYRIGHT, 1949

BY THE YORKE PUBLISHING COMPANY, INC.

All Rights Reserved

Editorial

Retrospect and Prospect, 1949

THE American Journal of Medicine with this issue initiates its fourth year of publication. The editor takes the occasion to report upon the progress and problems of the past year, and the plans for the forthcoming twelve months.

Friends of the Journal will be pleased to know that The American Journal of Medicine in the past year continued its steady growth and, indeed, appears already to have attained the largest circulation in its class of "independent" medical journals (i.e., journals not serving as official organs of medical societies) which are published monthly. This is an unexpected accomplishment, particularly within so short a time as three years.

Gratifying as is such growth, the really significant fact is that this popularity has been achieved without deviation from the avowed policy of the Journal to maintain the highest standards in publication of clinical research and in the presentation of advanced teaching programs from leading medical schools and hospital clinics. We have made no compromises whatever in this regard and, indeed, there is every indication that The American Journal of Medicine has found favor because it aims high. The rapid growth of the Journal would seem fully to vindicate this stringent policy and to demonstrate that there are real needs at this level which the Journal is helping to meet.

A feature of the Journal which has attracted widespread interest are the symposia, two of which appear each year. Their organization is delegated to some authority in the

field selected, who serves as guest editor, and they are planned with great care to stimulate as well as to inform. The subject matter usually deals with a discipline which should not be but often is divorced from the narrow channels of internal medicine, to the disadvantage both of the internist and the specialty discipline. Two exceptionally fine symposia of this kind appeared in The American Journal of Medicine in the past year, one on syphilis, the other on poliomyelitis; both especially designed for the needs of a general medical audience and from all accounts serving a most useful purpose. During the coming year symposia on diabetes and on infectious hepatitis have been scheduled and they are expected to maintain the high standards established by their predecessors.

The seminars are invited papers presenting different points of view on large and usually controversial issues of current interest, the final paper being assigned with the view of attempting to integrate the arguments previously presented. These articles appear in six consecutive issues of the Journal, one topic being covered every six months. During the past year two lively and illuminating series of seminars brought together the work and concepts of leaders in the fields of protein hydrolysates and of mechanisms of congestive failure, both series helping much to clarify thinking in these difficult subjects. The next series will deal with the newer antibiotics, the first contribution, by Dr. Waksman, appearing in this issue.

Each issue of the Journal also contains a review article on some topic of current interest. In the selection of these reviews preference has been given to those that assimilate rather than recite published data, presenting critically integrated and constructive points of view which may be more original than some so-called original reports and certainly more helpful in advancing knowledge and understanding; indeed, many of these reviews contain an abundance of new facts and ideas. Opportunity is afforded also for reasoned speculation and broad philosophic discussion for which a suitable outlet is so much needed.

The various Conferences remain the keystone of the teaching effort of the Journal. These combined staff conferences represent a peculiarly American contribution to medical pedagogy, a replacement of the star system, limited to a solitary presentation, by the team system coordinating the efforts of those with special interests and experience. The team approach brings to bear upon medical problems a fullness which one man alone can rarely approach and has the collateral advantage of providing common ground for different disciplines which otherwise tend to go their several ways to the detriment of progress both in medicine and in the basic sciences. Throughout the coming year The American Journal of Medicine will continue publication of the Cornell Conferences on Therapy, the Columbia Combined Staff Clinics, the Washington University Clinicopathologic Conferences and the Harvard Conferences on Psychosomatic Problems. Each of these conferences comes directly from the classrooms of the respective university hospitals represented; all are painstakingly planned and edited to make effective teaching exercises of sustained interest. It is hoped in this way to continue to exploit the opportunities presented by the Journal to extend facilities for instruction at a high postgraduate level.

An important function of The American Journal of Medicine is to publish the results of original clinical investigation. Here we have sought a middle ground between

highly specialized research of immediate interest to very few and repetitious accounts of clinical experiences already familiar to most. The chief difficulty of the editor in this regard has been to limit the acceptance of studies of the desired character and scope to the number that could be published within a reasonable time. The flow of fine papers from all parts of the country has been so heavy that it has, unfortunately, been necessary to turn away many meritorious studies simply because of limitations in space. Moreover, in order to ensure current interest it has been necessary to disregard the chronologic order of receipt of manuscripts and give precedence to those urgent communications which would suffer most by delay. These efforts have kept the Journal up-to-date and have resulted in a net shortening of the publication period but there is still a large backlog of manuscripts. Every effort is being made to expedite the publication of these articles.

In addition to formal presentations of the results of clinical research the Journal publishes in abstract form the scientific proceedings of various sections of the American Federation for Clinical Research, the Western Society for Clinical Research and the Southern Society for Clinical Research. These proceedings describe a wide variety of research activities and are of unusual interest. It is planned to continue their publication throughout the next year.

In concluding, the editor wishes to take this opportunity to express his indebtedness to the many who have contributed so generously of their time and energy to strengthen the effectiveness of the Journal in its various programs. Thanks are due also to the confidence and support of the growing host of friends whose interest in the Journal has ensured its success. It shall continue to be the endeavor of the publishers and the editorial board to maintain a position of respect and affection for The American Journal of Medicine among the established medical journals of the country.

ALEXANDER B. GUTMAN, M.D.

AMERICAN JOURNAL OF MEDICINE

Clinical Manifestations of Intercapillary Glomerulosclerosis in Diabetes Mellitus*

GEORGE V. MANN, M.D., CARL GARDNER, M.D. and HOWARD F. ROOT, M.D.
Boston, Massachusetts

THE fact that the presence of diabetes mellitus accelerates development of vascular sclerosis in humans has long been well established. The excessive frequency of advanced arteriosclerotic lesions commented upon by Aschoff,^{1,2} and

death in patients with diabetes emphasizes that with the availability of insulin and dissemination of the knowledge necessary for its proper use the number of deaths due to diabetic coma has steadily declined. Concomitant with this reduction in coma

TABLE I
INFLUENCE OF DURATION OF DIABETES MELLITUS UPON PERCENTAGE OF TOTAL DEATHS IN DIABETICS DUE TO ARTERIOSCLEROSIS AND TO DIABETIC COMA

	Average Duration of Diabetes (yr.)*	Deaths (total)	Coma (%)	Arterio-sclerosis (%)	Average Age at Death (yr.)
Naunyn 1898 to June, 1914.....	4.9	326	64	17	44.5
Allen June, 1914 to August, 1922.....	6.1	836	42	24	46.7
Banting August, 1922 to December 31, 1925.....	7.5	537	21	41	54.3
January, 1926 to December 31, 1929.....	8.4	918	11	49	60.0
January, 1930 to December 31, 1934.....	10.0	1741	5	58	62.7
January, 1935 to December 31, 1936.....	11.6	793	4	59	63.9
Hagedorn January, 1937 to December 31, 1939.....	12.4	1229	4	62	64.8
January, 1940 to December 31, 1943.....	13.3	1354	3	66	65.0
Charles H. Best January, 1944 to date.....	14.1	651	3	67	64.5

* Based on cases of known duration. Deaths reported through May 15, 1946. (Adapted from JOSLIN et al., 8th ed. Treatment of Diabetes Mellitus. Philadelphia, 1946. Lea and Febiger.)

demonstrated in the first and succeeding autopsy series at the New England Deaconess Hospital, has been noted by many writers.³ The premature development in diabetic youths of arteriosclerosis with renal and retinal lesions is well known.⁴ Consideration of statistical trends of causes of

deaths and the great prolongation of the lives of diabetics an increase has developed in the percentage of diabetic deaths due to arteriosclerosis. (Table I.)
With the advent of antibiotic therapy of infectious disease, the number of diabetics who survive these acute obstacles, only to

* From The George F. Baker Clinic, New England Deaconess Hospital and The Department of Medicine. Peter Bent Brigham Hospital, Boston, Mass. This work was supported by a grant from the Life Insurance Medical Research Fund.

die of one or another of the diseases secondary to arteriosclerosis, has steadily increased. However, the possibility of postponement of premature sclerotic lesions has been demonstrated by the absence of such lesions in twenty-eight of 192 childhood diabetics who survived twenty years of diabetes.⁵

The commonest cause of death in diabetes mellitus is disease of the coronary arteries.⁶ There is no reason to believe that coronary artery disease in diabetics differs in the histopathologic sense from the disease in non-diabetics. The same applies to sclerotic disease of the cranial vessels.

Renal disease as a complication of diabetes has attracted attention first, because of its steadily increasing frequency and second, because there is some evidence, both clinical and pathologic, to indicate that there may be a type of renal disease characteristic of patients with diabetes mellitus.

Interest in nephritis as a complication of diabetes was aroused in 1936 with the description by Kimmelstiel and Wilson⁷ of unusual lesions in the renal glomeruli of a small series of patients, most of whom were known to have been diabetic. These lesions consisted of depositions of faintly acidophilic, hyalinized material in the glomerular tufts. Similar lesions have since been described many times.⁸⁻¹⁰ There is no doubt now that indistinguishable lesions may occur occasionally in non-diabetic patients, nor do all diabetic patients inevitably develop these lesions. Estimates of the incidence of these lesions in diabetic patients vary from 18 to 63 per cent in surveys of autopsy material from various hospitals. The variation in these estimates would seem to be due largely to disagreement among pathologists as to the criteria to be employed in the anatomic diagnosis.

Kimmelstiel and Wilson, on the basis of experience with eight patients, described an associated triad of clinical findings: (1) a history of diabetes mellitus, (2) edema and (3) albuminuria. It now appears that the histologic lesions when found in the kidneys are not a specific indication of diabetes;

neither is the presence of diabetes with edema, albuminuria, hypertension and renal failure evidence that the anatomic lesions will invariably be found.¹¹

The classification of renal disease in diabetics has been obscured by the tendency to group all patients into two groups, chronic glomerular nephritis and chronic pyelonephritis. Acute glomerular nephritis in diabetics has been uncommon in the experience of this clinic. The significance of this fact is unknown. There is no question but that diabetics, particularly females, are especially susceptible to urinary tract infections. Autopsy material has confirmed the frequency of acute and chronic pyelonephritis.

Because of the increasing importance of renal disease in the management of diabetes and the unusual clinical material available in this clinic, we have undertaken a study of selected diabetic patients with renal disease in an attempt to clarify the clinical manifestations of this frequently fatal lesion. At present we know of no curative therapy. Renal or coronary artery disease represents the greatest menace to the young diabetic. There is no generally accepted means of delaying or alleviating these so-called "degenerative" diseases which eventually lead to a fatal outcome. Control of diabetes with a planned diet and insulin in the prevention of these complications has been considered of prime importance but the exact relationship between control of the diabetes and other factors, such as infection and abnormal endocrine states, has not been established. An answer to this question would be of extreme importance in the management of diabetic patients. Indeed, the diabetic patient with his known tendency to early and rapidly advancing vascular sclerosis offers an unusual opportunity for the study of both the etiology of arteriosclerosis and the factors which influence the course of this important disease. Recently Lukens¹² has described lesions similar to those characteristic of intercapillary glomerulosclerosis in the kidney of a dog kept diabetic for five years after injections of crude extract of

beef anterior pituitary. The study of vascular sclerosis is thus open to investigation in at least one species of lower animal.

PROCEDURE

In order to obtain an estimate of the relative incidence of the various types of renal complications in our diabetic population we have first studied the data available in the records of all patients discharged from the New England Deaconess Hospital in the year 1944 with a diagnosis stating or implying disease of the urinary tract. All of these admissions were of patients with diabetes. The previous records and subsequent developments were consulted and the patients were catalogued with the final diagnosis, which in many instances would be more accurate than the original clinical impression.

The data in Table II reveal an unusually high proportion of patients with the clinical manifestations of nephrosis, i.e., young patients with albuminuria, hypoproteinemia, often with edema and with clinical progression to hypertension and azotemia. To avoid the confusing term nephrosis and for reasons we shall set forth this syndrome will be referred to as intercapillary glomerulosclerosis.

Since many of the patients in this clinic have been followed for several decades, we were afforded an unusual opportunity to study the life history of their renal complications. We have, therefore, selected those patients from the 1943 to 1945 population who fulfilled the following qualifications: (1) Onset of diabetes mellitus before age thirty; (2) duration of diabetes mellitus of not less than ten years; (3) serial examinations over the course of their diabetic history extending from a period when renal function was normal to the presence of unmistakable impairment of renal function or death; (4) clinical evidence supporting a diagnosis of intercapillary glomerulosclerosis. From the three-year hospital population we have selected forty-three patients who fulfill these qualifications.

Through study of this selected group of patients we were able to evaluate the significance of duration of diabetes, of degree of control and of severity of diabetes, in addition to the chronology of onset of such specific symptoms as hypertension, albuminuria, edema, azotemia and other laboratory evidence of impairment of renal function.

The records of this group of forty-three patients were summarized in tabular form. In some instances hospital admissions were arranged in order to complete the serial study. The data have been studied and evaluated in comparison with the characteristics of the

TABLE II
SUMMARY OF DIABETIC PATIENTS DISCHARGED FROM THE
JOSLIN SERVICE IN THE PERIOD JANUARY 1, 1944
TO DECEMBER 31, 1944

	No.	Per Cent of Total
Total no. patients.....	1,708	
Male.....	685	40
Female.....	1,023	60
Patients with proven urinary tract disease.....	83	4.9

Type of Urinary Tract Disease	No.	Per Cent of Total with Renal Disease
Cystitis*.....	10	12.1
Lithiasis (of the kidney, ureter or bladder).....	10	12.1
Pyelitis and pyelonephritis.....	21	25.2
Vascular nephritis†.....	12	14.5
Nephrosis (? intercapillary glomerulosclerosis).....	17	20.5
Toxic nephritis‡.....	1	1.2
Anatomic aberrations—leading to disease.....	4	4.8
Idiopathic edema (without demonstrable renal lesions).....	1	1.2
Acute glomerular nephritis.....	2	2.4
Miscellaneous§.....	5	6.0

* This diagnosis was made only in the presence of pyuria, positive urine cultures and with a demonstrable systemic reaction, i.e., fever or urinary symptoms. If pyuria and positive cultures alone were used as the criteria, the incidence would be much higher, particularly in females.

† This diagnosis was made according to Volhard and Fahr's definition of "nephrosclerosis."

‡ In this case due to sulfonamides.

§ Including one case of toxemia of pregnancy with apparent recovery, one case of renal amyloidosis, one case of hepatorenal failure, one case of coma with anuria and one case of hematuria of unknown etiology.

1944 hospital population used as a reference group and the following attributes of the study group itself have been summarized: (1) Sex

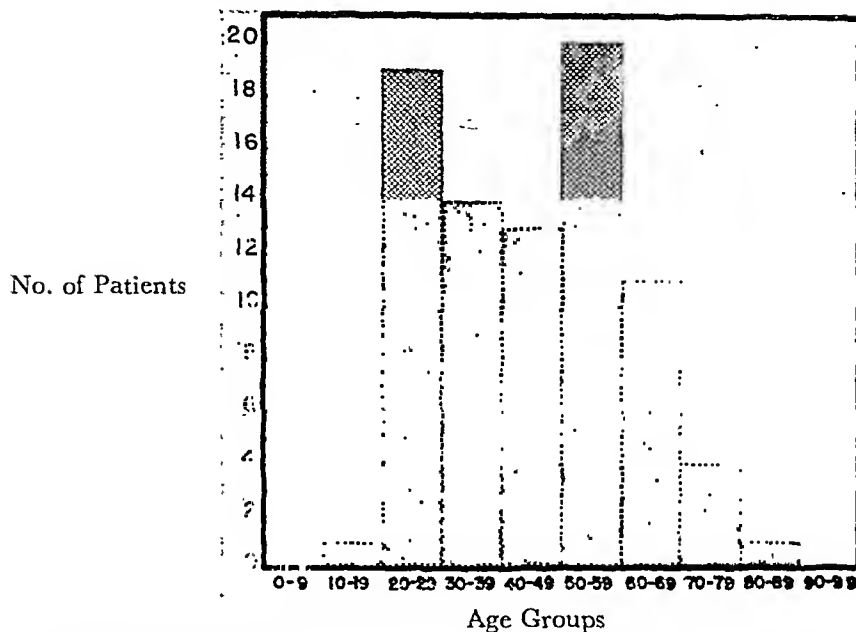


FIG. 1. Age distribution of eighty-three patients with urinary tract disease; 1944 hospital population.

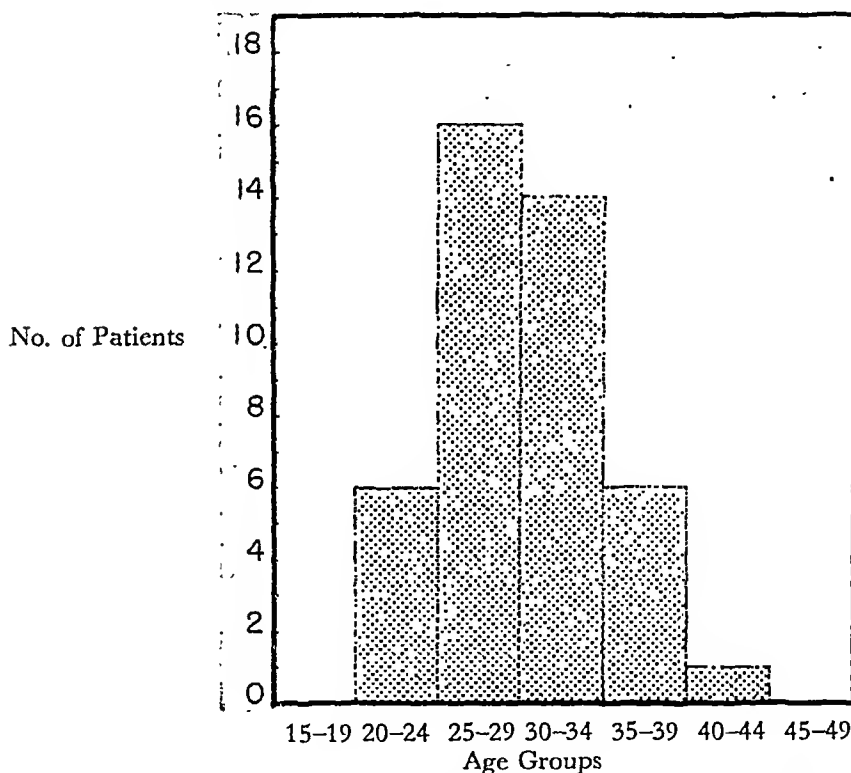


FIG. 2. Age distribution of forty-three patients with intercapillary glomerulosclerosis.

Figure 2 illustrates the age distribution at the time of study of the entire group of forty-three patients diagnosed as having intercapillary glomerulosclerosis. Since these patients are age-selected cases as just described, this distribution is not strictly comparable with the entire hospital population. However, our experience indicates that the syndrome is not found frequently in patients over forty years of age.

Duration of Diabetes. Few of the anatomic studies have emphasized the significant relation between duration of diabetes and development of vascular complications. The records of this hospital are especially valuable because a large group of young diabetics has been followed for several decades and particular emphasis has been placed upon determination of the time of onset of diabetes mellitus. Juvenile diabetes

is in addition more easily dated because of the acute manifestations and the presence of parental observers.

In the group of forty-three patients studied the average age at the onset of the diabetes was 15.8 years and the average

studied. A somewhat more objective method may be the history of diabetic coma. Of the patients studied 37 per cent were in diabetic coma on at least one occasion. In this clinic that is considerably above average. On the other hand, there is no known

TABLE V
ESTIMATE OF SEVERITY OF DIABETES MELLITUS

Severity	Daily Insulin Dose (units)	No. Patients	Per Cent of Total
1 plus	0-20	3	7
2 "	20-40	23	53
3 "	40-60	15	35
4 "	60+	2	5

duration of diabetes at the appearance of the first sign of renal disease was 14.8 years.

Severity of Diabetes. Previous reports have emphasized that renal complications occur more commonly in patients with mild diabetes. Our experience does not confirm this observation. Table v indicates that the diabetes in our series was severe, as indicated by insulin requirement.

Degree of Control of Diabetes. It is of crucial importance to the management of diabetics to know the relationship of diabetic control to development of irreversible complications. Various opinions are held.^{13,14} The answer is in part complicated by the difficulty in clinical practice of accurately determining for long periods of time the degree of control which is achieved. The outstanding facts presented by Priscilla White in her study of 192 diabetic children who survived twenty years of diabetes are: (1) Of fifty patients incapacitated by nephritis, retinitis and coronary disease 75 per cent had been in coma one or more times. (2) Of 114 patients with moderate lesions (a few retinal hemorrhages, calcified arteries) 50 per cent had had coma. (3) In twenty-eight patients without arteriosclerosis coma had been present in only 17 per cent.

Table vi lists our appraisal of the degree of control achieved in the group of patients

TABLE VI
ESTIMATE OF DEGREE OF CONTROL OF DIABETES MELLITUS
Fair*..... 55 per cent
Poor*..... 45 per cent

	No.	Per Cent of Total
Patients never in coma.....	27	63
One episode of coma.....	8	19
Two episodes of coma.....	4	9
More than two episodes of coma.....	4	9
	43	

* Clinical appraisal based upon urine and blood glucose levels upon admission.

young patient with comparably severe diabetes who has escaped arteriosclerotic complications while maintaining poor control of his disease.

CLINICAL MANIFESTATIONS

The correlation between the clinical manifestations of renal complications in diabetes and the anatomic findings is good only when the renal lesions are far advanced. Thus Henderson *et al.*¹¹ found that intercapillary glomerulosclerosis could be predicted with a fair degree of certainty in a diabetic of long duration with albuminuria, hypertension, renal insufficiency and retinopathy. These authors found that patients with retinopathy involving the veins, with or without proliferative changes, invariably showed intercapillary glomerulosclerosis at autopsy.

Figure 3 summarizes the frequency of clinical manifestations in the patients we have studied. Since the patients were in various stages of development of the renal complication (40 per cent dead), it will be recognized that the incidence of these manifestations will increase. The universal appearance of albuminuria and hyperten-

sion is consistent with other reports. The frequency of retinitis and particularly of retinitis proliferans, equivalent to Wagener's Group IV,¹⁵ suggests a correlation between this clinical syndrome and the renal disease. Somewhat fewer of these patients exhibited cardiac signs or symptoms than in other reports. We believe this may be explained by the considerably younger age group studied. This would seem to imply that the renal vessels are more susceptible than the coronary vessels in younger patients, or the explanation may lie in the superimposition of this arteriolar disease upon the arterial sclerosis commonly seen in non-diabetic patients with advancing age, in the latter instance making the heart and great vessels more vulnerable.

Volhard and Fahr¹⁶ and later Addis and Oliver¹⁷ emphasized the importance of red blood cells in the urinary sediment in distinguishing chronic glomerular nephritis from nephrosclerosis. These and most subsequent authors agree that hematuria is infrequently found in the course of nephrosclerosis and when found the number of red cells is small. In contrast, hematuria, usually massive in amount, is characteristic of all stages of glomerular nephritis, with the occasional exception of the recovery stage when hematuria disappears before the casts and proteinuria. Proteinuria in nephrosclerosis is also generally less than in glomerular nephritis, rarely exceeding 2 Gm. per twenty-four hours and generally less than 1 Gm. per twenty-four hours. In the diabetic group studied here proteinuria was an early finding and typically averaged 3 to 10 Gm. per twenty-four hours after the first few months.

The character of the urinary sediment in diabetic patients is often affected by lower urinary tract infection but study of these patients indicated first that red blood cells or cellular casts were generally absent and when present were few in number. Casts were frequent but in small numbers and almost always of the hyaline type with typical broad, hyaline "renal failure" casts terminally.

Edema also is infrequent in nephrosclerosis unless cardiac failure is responsible. Edema was a frequent early symptom in the diabetic group studied and in the females was often the first sign observed.

Anemia in these patients did not appear

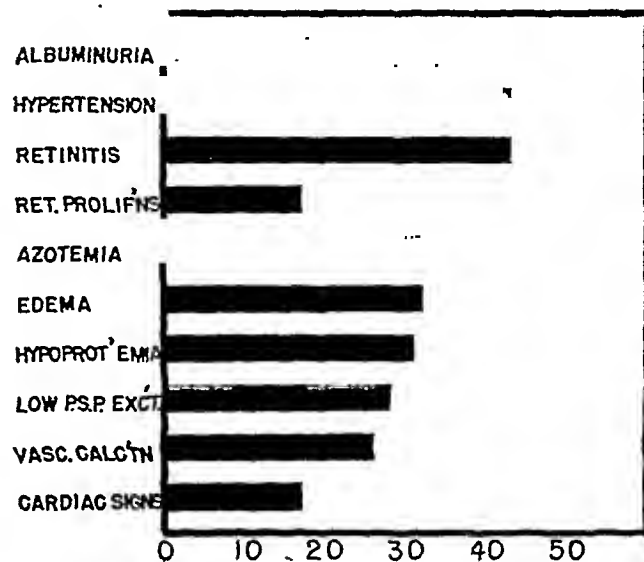


FIG. 3. Frequency of manifestations.

until late in the course of the renal disease, in contrast to the expected course of chronic glomerular nephritis. In these patients the onset of significant anemia coincided with the appearance of azotemia. In only three of the forty-three patients did the hemoglobin fall below 10 Gm. per cent or the red blood cell count below three million per cu. mm. during the course of the disease.

Despite the massive proteinuria, hypoproteinemia was a relatively late and generally terminal finding. A typical terminal value of 4 Gm. per cent with an albumin globulin ratio of 1 was found. Apparently these patients, who maintain good appetites until uremia occurs and are maintained on adequate diets, are able to synthesize new protein to compensate for the large amount lost in the urine. The lack of correlation between serum protein levels and the onset of edema was striking in contrast to the findings in nephrosis or the degenerative nephritis of Addis.

The implication of faulty cholesterol metabolism in the tendency to development of vascular sclerosis among diabetics

suggested a compilation of the serum cholesterol observed in this group of patients. There were twenty-two patients in the study group with adequate serial observations of the cholesterol level in the blood. With one exception, these values

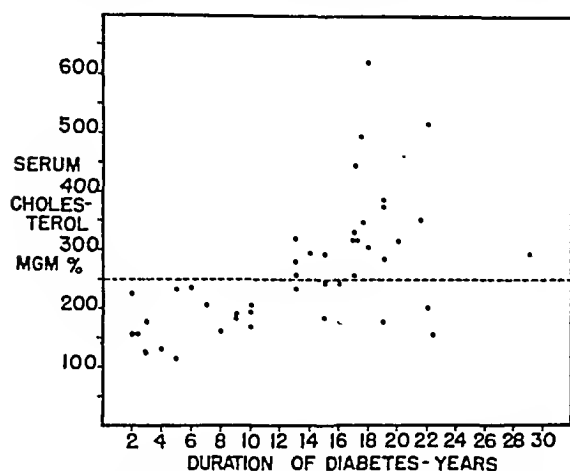


FIG. 4. Relationship of serum cholesterol to duration of diabetes in twenty-two patients with intercapillary glomerulosclerosis.

were all below the accepted maximal normal of 250 mg. per cent when the patients were first seen, and the excepted patient's level became normal within a few days after treatment with insulin. As illustrated in Figure 4 the cholesterol levels remained within normal limits for the first ten years of the disease. After this time, coinciding with the development of clinical manifestations of intercapillary glomerulosclerosis, there was an increase of serum cholesterol in all but three of the patients. We have no certain means of distinguishing cause from effect but are inclined to believe this elevation of serum cholesterol may be associated with the renal and vascular disease for two reasons: (1) The cholesterol abnormality appears almost simultaneously with or after other destructive signs or symptoms of renal complications. (2) The elevation of cholesterol correlates well with the fall in serum proteins. This inverse relationship of total serum protein concentration to serum cholesterol concentration is seen, however, in other forms of renal disease, notably nephrosis, in which vascular sclerosis is not found. The influence of

this cholesterol abnormality upon development of vascular sclerosis and intercapillary glomerulosclerosis is still to be determined.

Table VII illustrates the chronologic life history of the renal complications as manifested in this group of patients. Those pa-

TABLE VII
RELATIONSHIP OF CLINICAL MANIFESTATIONS
AND LABORATORY FINDINGS TO AGE AND
DURATION OF DIABETES MELLITUS

Manifestation	No. Patients Examined*	Average Age at Onset of Manifestation (yr.)	Average Duration of Diabetes at Onset of Manifestation (yr.)
Albuminuria.....	40	26.0	15.0
Edema.....	32	29.0	15.9
Hypertension.....	40	28.8	16.1
Impaired PSP excretion.....	28	29.5	17.2
Azotemia.....	33	33.3	17.8
Hypoproteinemia..	31	30.2	17.8
Calcification of vessels visible by x-ray.....	30	18.0

* Only those patients are included in whom the age at onset could be determined with accuracy.

tients whose records did not furnish accurate evidence of the time of onset of a particular manifestation were excluded from consideration in this tabulation.

We are led to conclude that there is a natural sequence of events in development of this renal complication. The earliest manifestation is albuminuria, at first small in amount and transient, later becoming permanent and massive. Edema is not consistently related to the level of serum proteins, hypoproteinemia developing considerably later than edema. Edema also is intermittent initially. Hypertension occurs early and in our experience is often not of extreme degree until late in the course of the disease. We have been impressed with the number of patients who exhibit loss of phenolsulfonphthalein clearance and show hyposthenuria at a late stage of the disease.

Studies are continuing in an effort to establish whether renal tubular function is

preserved after a demonstrable reduction of glomerular filtration rate. It would be of interest to know whether the anatomic specificity of the most obvious lesion determines the limitation of a specific renal function, namely, glomerular filtration.*

FATAL CASES OF RENAL DISEASE COMPLICATING DIABETES

Of the forty-three patients selected for study sixteen are now dead. Table VIII summarizes these cases.

TABLE VIII
SUMMARY OF SIXTEEN FATAL CASES OF RENAL DISEASE COMPLICATING DIABETES

Case No.	Sex	Age at Onset of Diabetes (yr.)	Duration of Diabetes at First Renal Signs (yr.)	Duration of Life after Onset of Nephrosis (yr.)	Duration of Diabetes at Death (yr.)	Age at Death (yr.)	Immediate Cause of Death	Autopsy	Presence of Lesions of I.C.G.*
6208	M	12	18	2	20	32	Pulmonary edema	x	x
4768	M	10	16	7	23	33	Cerebral embolus	x	x
7795	F	15	11	7	18	33	Renal failure	x	x
6346	M	12	9	9	18	30	Myocardial infarction	x	x
6033	M	21	12	7	19	40	Renal failure	x	x
7695	F	17	11	5	15	33	Sepsis and myocardial infarct	x	0
3761	F	9	18	3	21	30	Congestive failure	x	x
8405	M	10	10	6	20	26	Postoperative shock	x	x
2726	M	14	16	9	25	39	Renal failure	0	?
13272	M	9	9	5	14	23	Renal failure	0	?
10999	M	24	9	6	15	39	Renal failure	0	?
4746	M	13	7	11	18	31	Congestive failure	0	?
5635	F	13	7	12	19	32	Renal failure	0	?
10270	M	7	16	4	20	27	Renal failure	0	?
5036	M	9	18	2	20	29	Renal failure	0	?
7966	M	10	14	8	22	32	Renal failure	0	?
Average	..	12	12	6.4	19	32			

* Intercapillary glomerulosclerosis.

Dolger⁴ has pointed out that calcification of peripheral vessels demonstrable by x-ray is a relatively late and inaccurate sign of vascular damage. Our evidence supports this view. However, the value of this sign is determined by the diligence with which it is sought. Our continuing studies include regular and extensive x-ray examination of the most frequent sites of calcification, notably the legs and pelvis.

* Since this article was written Corcoran *et al.* have published studies on the renal hemodynamics in intercapillary glomerulosclerosis which tend to substantiate this hypothesis. CORCORAN, A. C., TAYLOR, R. D. and PAGE, I. H. Functional patterns in renal disease. *Ann. Int. Med.*, 28: 576, 1948.

This group is composed of twelve males and four females, a distribution which is consistent with the preponderance of males in the entire group. The average age of the onset of diabetes was approximately 12.4 years in the fatal cases, coinciding with the observation that in children diabetes is most frequently first observed during puberty. The study group of patients did not include an unusual number of "diabetic dwarfs" or other evidences of endocrinologic disorders. The average duration of diabetes when the first renal abnormality was noted shows considerable variation. It is apparent, however, that these young patients had developed extensive vascular damage as judged by renal function in a period of 12.5 years after the onset of diabetes and are at age twenty-five

comparable in this respect with non-diabetic patients of over twice this chronologic age. In the majority of these patients the first clinical sign of renal damage was proteinuria although in a few, particularly the females, edema was the first sign. The short duration of life (average 6.4 years) after the appearance of the first signs of renal disease, although quite variable, serves to emphasize the malignity of this complication.

There were eight autopsied cases, seven of which showed some degree of intercapillary glomerulosclerosis. In the seven cases in which the anatomic diagnosis was established the average duration of life after the first renal sign appeared was 5.9 years. The average duration of diabetes at death for this group was 19.0 years and the average age at death thirty-two years.

Cases 6208 and 4768 in Table VII are of particular interest since these patients were identical twins. Diabetes was diagnosed at ages twelve and ten years, respectively, and the clinical courses were remarkably similar. Severity of diabetes was similar in both patients. Control of the disease was only fair in each case although neither patient was known to have been in a diabetic coma. The terminal events in case 4768 were complicated by peripheral vascular occlusions requiring amputations. Autopsy examination revealed extensive arteriosclerosis in both patients with both atherosclerotic and arteriolar changes. In case 6208 typical advanced lesions of intercapillary glomerulosclerosis were found with extensive arteriosclerosis and atherosclerosis. There was moderate renal interstitial fibrosis and inflammation. Case 4768 showed fresh renal infarctions with extensive arteriosclerosis. The degree of arteriosclerosis masked the typical intercapillary lesions but in some glomeruli characteristic lesions were found. These two patients with a common genetic background illustrate the anatomic variations along a single pattern which may develop in diabetes of long duration.

With the exception of case 7695 the remaining five autopsied cases all showed four distinctive lesions in the kidneys: atherosclerosis, arteriosclerosis, interstitial inflammation with fibrosis and intercapillary glomerulosclerosis. The degree of each of these changes was variable. Far advanced arteriosclerosis tended to obscure the characteristic changes of intercapillary glomerulosclerosis. Case 6033, on the other hand, was characterized by vascular lesions predominantly in the form of inter-

capillary glomerulosclerosis. The evidences of pyelonephritis were slight and limited to an interstitial inflammatory reaction with scattered areas of fibrosis. The distinction of the histologic lesions in these patients from the lesions of glomerular nephritis was easily apparent. However difficult the problem of determining the earliest anatomic signs of intercapillary glomerulosclerosis may be, absence of the classical signs of glomerular nephritis allows immediate elimination of this diagnosis.

Case 7695 was distinctively typical, histologically, of chronic glomerular nephritis. A moderate degree of arteriosclerosis and atherosclerosis was also present and a small amount of interstitial infiltration indicated the presence of mild pyelonephritis. In retrospect, the clinical course of this patient should have betrayed the type of renal disease present. Although no acute episode of glomerulonephritis was recognized, the onset of massive albuminuria, hypertension and hematuria with casts was almost simultaneous. The hypertension became severe within a few months. Marked anemia appeared in the early stages. Phenolsulfonphthalein clearance fell early and within two years after the first recognized renal signs the patient was in typical uremia. Cardiac decompensation was present when edema first appeared.

The course and histologic findings of this patient thus serve to contrast the picture of chronic glomerular nephritis with that of the distinctive picture seen in the remaining cases.

Using these data as a guide we may postulate a hypothetical "typical" case which would represent the average performance of this group.

A thirteen year old child develops moderately severe diabetes requiring 40 to 60 units of insulin per day for adequate control on a regulated diet. Management of the disease is only fair and diabetic coma will probably occur. Thirteen years later at the age of twenty-six the first signs of renal damage appear, with an insidious and often intermittent proteinuria. After a few months this becomes constant and increases in amount to 3 to 10 Gm. per twenty-four hours. The urine sediment reveals numerous hyaline casts and occasionally small numbers of red blood cells. These signs are followed by intermittent

edema and hypertension, both mild in degree. Punctate hemorrhages are found in the eye grounds. In two years proteinuria, edema and hypertension are well established, the serum non-protein nitrogen is now elevated, the serum albumin fraction falls and the phenolsulfonphthalein excretion becomes moderately reduced. The patient often complains of poor vision and examination reveals retinitis proliferans—usually bilaterally. Careful x-ray examination will generally reveal calcification of peripheral vessels or occasionally of the vas deferens in males.

The terminal two to three years lead to progressive deterioration with persistent uremia, edema, hypoproteinemia and anemia. Death is usually caused by myocardial infarction, congestive failure or a result of renal failure and uremia. In the last few months the diabetes is controlled with great difficulty. The patients are often blind at death with hemorrhagic glaucomas.

The association of these characteristic clinical manifestations with the remarkable prematurity of vascular sclerosis, and particularly with the glomerular lesions previously described in diabetics of long duration, lead us to believe that the clinical course and anatomic changes represent a distinctive entity. Just as the glomerular lesions may be found occasionally in non-diabetics, so the clinical findings may suggest a true chronic glomerulonephritis and be misleading.

The relationship of this peculiar renal complication of diabetes to nephrosclerosis is not clear. The disparity in the age of the diabetic group when compared with the older patients usually seen with nephrosclerosis suggests that the two are fundamentally different diseases. However, the well known tendency of youthful diabetics to "age" rapidly, with early appearance of signs of vascular sclerosis, may make a consideration of chronologic age in these patients misleading. Indeed, the situation implies that calculation might be made using chronologic age and diabetes duration which would allow one to arrive at a

"true age" from these data. Until and unless this is done it would seem fallacious to draw conclusions from chronologic age data.

Duration of the disease, nature of the urine sediment, mild anemia and associated cardiovascular changes suggest the similarity of this disease of diabetics to the malignant form of nephrosclerosis seen in non-diabetics. However, the early onset of edema and the massive proteinuria serve to distinguish the two forms of renal disease. That these distinctions represent the influence of the youth of the patient substratum and other unknown influences of associated endocrine abnormalities remains uncertain. Until these factors are clarified it seems profitable to consider intercapillary glomerulosclerosis as a distinct entity both clinically and pathologically.

We know of no preventive measures other than continual and careful control of the diabetes with insulin, diet and exercise. Therapy after the disease has appeared is symptomatic. Perhaps the most hopeful aspect of this problem lies in the suggestions and material which it contributes to the study of arteriosclerosis and the biologic phenomena of aging.

SUMMARY

1. The records of all patients with urinary tract disease admitted over a period of one year to a hospital medical service specializing in diabetes have been studied and the types of renal disease classified.

2. The incidence of a characteristic syndrome consisting of proteinuria, edema, hypertension and retinitis occurring in young people with diabetes of long duration, is determined. Although the prognosis in the past has been grave, hope for future improvement by better control of diabetes and its complications is well founded.

3. A group of forty-three patients exhibiting this renal complication of diabetes has been studied and the usual course of the disease described.

4. The correlation of these clinical manifestations with the distinctive anatomic lesions often seen in the renal glomeruli of diabetic patients is discussed.

Acknowledgment. We are grateful to Dr. Jane Worcester of the Department of Biostatistics, Harvard School of Public Health, and to Dr. James P. O'Hare, Department of Medicine, Peter Bent Brigham Hospital, for advice in the preparation of this paper.

REFERENCES

1. ASCHOFF, L. Lectures on Pathology. P. 131. New York, 1924. Paul B. Hoeber, Inc.
- 2a. ROOT, H. F. and WARREN, S. A clinical and pathological study of twenty-six cases of diabetes. *Boston M. & S. J.*, 194: 45-53, 1926.
- 2b. WARREN, S. The Pathology of Diabetes Mellitus. 2nd ed., p. 121-131. Philadelphia, 1938. Lea & Febiger.
- 3a. JOSLIN, E. P. et al. Treatment of Diabetes Mellitus, 4th ed., pp. 675-708, 1928; 5th ed., pp. 324-345, 1935; 6th ed., pp. 380-405, 1937; 7th ed., pp. 419-437, 1940; 8th ed., pp. 481-503, 1946. Philadelphia. Lea & Febiger.
- 3b. DRY, T. J. and HINES, E. A. The role of diabetes in the development of degenerative vascular disease with special reference to the incidence of retinitis and peripheral neuritis. *Ann. Int. Med.*, 14: 1893-1902, 1941.
- 3c. WILDER, R., Clinical Diabetes Mellitus and Hyperinsulinism, P. 327, Philadelphia, 1940. W. B. Saunders Co.
- 4a. WHITE, P. In JOSLIN, et al. Treatment of Diabetes Mellitus. 8th ed., pp. 761-764. Philadelphia, 1946. Lea & Febiger.
- 4b. DOLGER, H. Clinical evaluation of vascular damage in diabetes mellitus. *J. A. M. A.*, 134: 1289-1291, 1947.
- 4c. Editorial. Diabetes and arteriosclerosis in youth. *J. A. M. A.*, 135: 1074, 1947.
5. WHITE, P. and WASKOW, E. Clinical pathology of diabetes in young patients. *South. M. J.*, 41: 561, 1948.
6. ROOT, H. F. In Treatment of Diabetes Mellitus by JOSLIN, et al. 8th ed. Philadelphia, 1947. Lea & Febiger.
7. KIMMELSTIEL, P. and WILSON, C. Benign and malignant hypertension and nephrosclerosis; intercapillary lesions in the glomeruli of the kidney. *Am. J. Path.*, 12-45: 83, 1936.
8. NEWBURGER, R. A. and PETERS, J. P. Intercapillary glomerulosclerosis. *Arch. Int. Med.*, 64: 1252, 1939.
9. SIEGAL, S. and ALLEN, A. C. Intercapillary glomerulosclerosis (Kimmelstiel-Wilson) and the nephrotic syndrome in diabetes mellitus. *Am. J. M. Sc.*, 201: 516-527, 1941.
10. LAIPPLY, T. C., EITZEN, O. and DUTRA, F. R. Intercapillary glomerulosclerosis. *Arch. Int. Med.*, 74: 354, 1944.
11. HENDERSON, L. L., SPRAGUE, R. G. and WAGENER, H. P. Intercapillary glomerulosclerosis, *Am. J. Med.*, 3: 131-144, 1947.
12. LUKENS, F. D. W. and DOHAN, F. C. Experimental pituitary diabetes of five years duration with glomerulosclerosis. *Arch. Path.*, 41: 19, 1946.
13. BOYD, J. D., JACKSON, R. L. and ALLEN, J. H. Avoidance of degenerative lesions in diabetes mellitus. *J. A. M. A.*, 118: 694-696, 1942.
14. LICHTENSTEIN, A. Treatment of children's diabetes; ten years' experience without dietetic restrictions, *Acta. Paediat.*, 32: 556, 1945.
15. WAGENER, H. P., DRY, T. J. and WILDER, R. M. Retinitis in diabetes. *New England J. Med.*, 211: 1131-1137, 1934.
16. VOLHARD, F. and FAHR, T. Die Brightsche Nierenkrankheit. Berlin, 1914. Julius Springer.
17. ADDIS, THOMAS and OLIVER, JEAN. The Renal Lesion in Bright's Disease, New York, 1931. Paul B. Hoeber, Inc.

Experiences with the Kolff Artificial Kidney*

ALFRED P. FISHMAN, M.D.,† IRVING G. KROOP, M.D.,‡ H. EVANS LEITER, M.D.

Chicago, Illinois

New York, New York

New York, New York

and ABRAHAM HYMAN, M.D.

IN March, 1947, Dr. W. J. Kolff brought to Mt. Sinai Hospital an artificial kidney devised by him.¹ We are presenting our experiences in the management of six patients who have been treated with this artificial kidney. At first we were reluctant to expose our patients to a new form of treatment with which we were relatively unfamiliar. Moreover, we had learned that a poor prognosis in acute toxic nephrosis often proves to be unwarranted; satisfactory results obtained by conservative management of such patients have been recorded elsewhere.²⁻⁴ We have stressed the possibility that diuresis may occur spontaneously. However, if this apparatus could contribute to the maintenance of metabolic equilibrium and sustain the patient until spontaneous diuresis should occur, it would be a valuable adjunct in the treatment of acute anuria.

All six patients who were treated by use of the artificial kidney were critically ill. The first four were dying of uremia. All conservative measures had been ineffective. These patients made it possible to test the capabilities of the apparatus without incurring risk of influencing the clinical course adversely. As the functional capacity of the machine and its efficacy were established the last two patients, although critically ill, were treated earlier than the others and they recovered. It is impossible to state whether spontaneous recovery would have occurred without use of the apparatus.

The possibility of removing various toxic products by dialysis has interested investigators for many years.⁵ Some have advo-

cated use of viable tissue membranes for dialysis.^{6,7} Peritoneal lavage has recently been revived by Fine and Seligman.^{8,9} The difficulties of the method are well known to those who have attempted this form of dialysis;¹⁰ they include peritonitis, obstruction of the inlet tube, difficulty in maintenance of flow and the long period of time involved. Use of an exteriorized intestinal loop and irrigation by a Miller-Abbott tube, and colonic irrigation have also been attempted, with varying degrees of success.¹¹⁻¹⁴

In 1912 Abel, Rowntree and Turner dialyzed the blood of living animals through collodion tubes, using hirudin as an anticoagulant.⁵ Haas, Necheles and Thalhimer¹⁵ extended these experiments. Kolff¹² described the first mechanical apparatus to permit continuous extracorporeal dialysis. Subsequently Alwell^{16,17} and Murray¹⁸ presented other devices. They have all taken advantage of the availability of cellophane and the reliability of heparin. Their machines make possible the dialysis of regulated volumes of blood outside of the body without danger of infection or coagulation. Each has attempted to achieve a maximum surface area of exposed blood per unit volume. Our experience is confined to the apparatus of Kolff.

METHODS AND MATERIALS

The basic mechanisms of the artificial kidney devised by Kolff are illustrated in Figures 1 and 2. The blood is rendered incoagulable by heparin. The blood is then delivered under the drive of arterial pressure to the coils of cellulose

* From the Medical and Genito-urinary Services, Mount Sinai Hospital, New York, N. Y.

† Formerly Dazian Foundation Research Fellow in Pathology.

‡ Dazian Foundation Research Fellow in Medicine.

acetate (Visking) tubing tightly wound about a rotating drum. The capacity of this machine is 500 to 700 cc. of blood. A special coupling serves as a conduit to enable the blood to enter and leave the cellulose acetate tubing without interfering with the rotation of the drum. Prior

the individual needs of the patient. In addition a shunting circulation is provided which permits circumvention of the dialyzing portion of the apparatus and enables direct intravenous administration of drugs, blood, etc., should the need arise. The glass arterial and venous can-

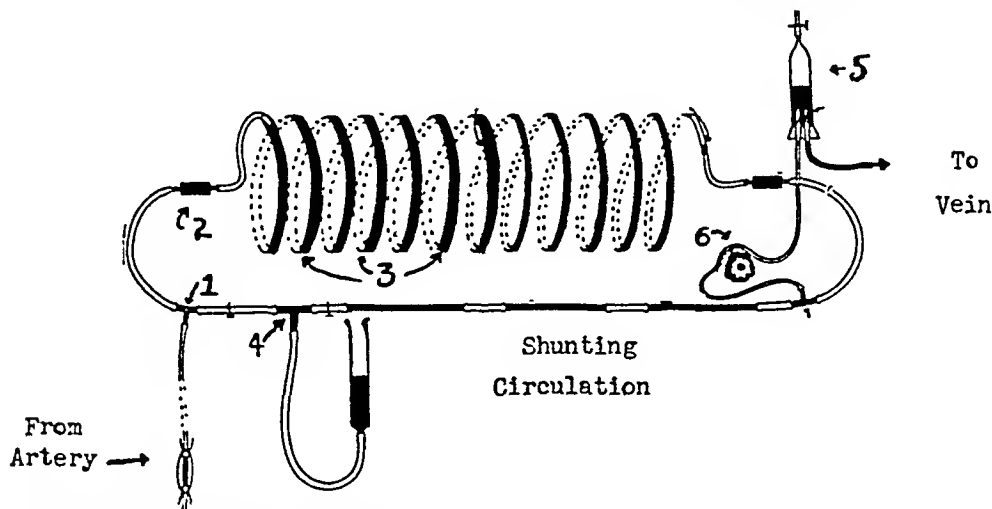


FIG. 1. The circulation of the artificial kidney (modified after Kolff). The blood leaves the radial artery and is led by connecting tubes (1) through the special coupling (2) into the coils of cellulose acetate (3) which are wound around the rotating drum. Fluids or drugs may be administered through a special connection (4) which allows the administered fluids either to pass through the kidney or be shunted directly into the vein of the patient. After dialysis the blood passes to a clot remover and air trap (5) before returning to the patient's vein. A mechanical pump (6) facilitates the emptying of the last coils of the artificial kidney.

to the start of treatment the tubing is filled either with heparinized whole blood or normal saline solution, depending on the hematologic needs of the patient. The blood from the radial artery displaces the contents of the system of tubing. A milking pump at the end of the system facilitates return of the blood to the patient's vein via an air trap and clot remover. While the blood is passing through the coils of cellulose acetate, the rotation of the drum intermittently exposes it to 100 L. of bath fluid which contains 0.6 per cent sodium chloride, 0.2 per cent sodium bicarbonate, 0.04 per cent potassium chloride and 1.5 per cent glucose. Calcium is not added to the bath since a precipitate of calcium carbonate would form. Consequently calcium gluconate is administered intravenously at regular intervals to replace the dialyzable calcium which escapes into the bath. Thus, under the continued influence of arterial pressure, gravity and a milking pump, blood is led from the radial artery to a brachial vein via an extrinsic vasculature made of cellulose acetate. During circulation it is exposed to a bathing solution which may be varied according to

nulac prescribed by Kolff were found to be unnecessary precautions against coagulation and were discarded in favor of ordinary metal intravenous needles. At regular intervals chemical analyses were made of blood entering and leaving the apparatus as well as of the bath fluid. These included blood urea nitrogen (Van Slyke and Cullen), creatinine (Folin and Wu), uric acid (Brown), glucose (Folin and Wu), serum protein (Kagan), serum chloride (Van Slyke and Sendroy), icterus index (Newburger), bilirubin (van den Bergh), calcium (Kramer and Tisdall), inorganic phosphorus (Kuttner and Lichtenstein), sodium (Butler).¹⁹

CASE REPORTS

CASE 1. E. R. is a Puerto Rican woman twenty-five years of age. On January 5, 1948, twenty-one days before admission to the Mount Sinai Hospital, she was raped. On the evening of January 21st, when the anticipated menstruation failed to occur, she inserted 5 sublimates of mercuric tablets (2.5 Gm.) into the vagina in order to induce abortion. Several hours later abdominal pains appeared. By the

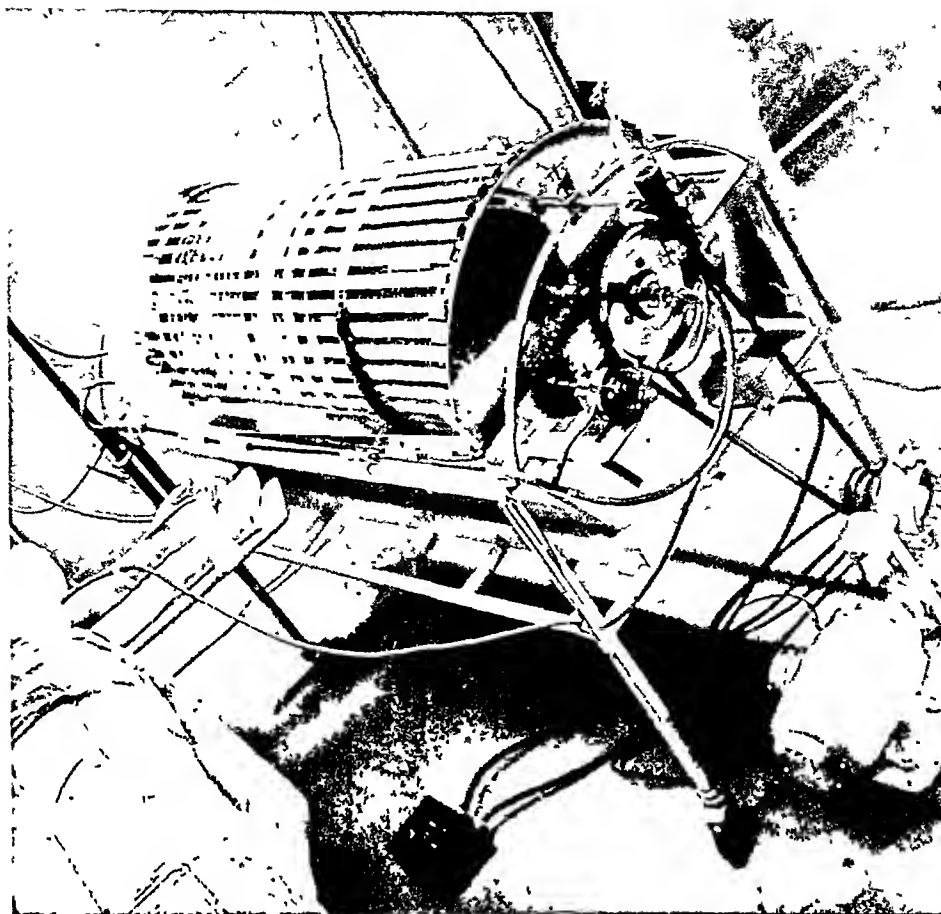


FIG. 2. The artificial kidney in use.

next morning she was acutely ill, with abdominal pain, bloody diarrhea, frequent vomiting and profuse vaginal bleeding. On January 23, 1948, she was admitted to the gynecologic service of another hospital. The temperature was 100.8°F., the pulse was 86 and the respirations 20 per minute. Blood pressure was 112 mm. Hg systolic and 84 mm. diastolic. Intense vulvovaginal edema and necrosis were present. At this time analyses revealed a hemoglobin of 16 Gm., 23,600 white blood cells with 73 segmented and 22 non-segmented leukocytes and 7 lymphocytes. The serum non-protein nitrogen was 75 mg. per cent. Bloody diarrhea and vomiting continued. Pain, swelling and tenderness of the joints of the fingers appeared and progressed. Twenty-four hours after admission it was noted that the patient failed to urinate. No urine could be obtained by catheter. A history of anuria since January 22nd was then elicited. The patient was thereupon transferred to the Mount Sinai Hospital on January 26th for treatment with the artificial kidney. Up to this time she had received approximately 7,000 cc. of fluid by vein and hypodermoclysis.

Examination revealed a poorly developed, poorly nourished, semicomatose Puerto Rican

woman in acute distress. She was vomiting coffee-ground material and blood was oozing from her mouth and gums. She looked pale and her face was edematous. The temperature was 98.2°F.; the pulse was 90 and the respirations 18 per minute. Moderate bilateral conjunctivitis and chemosis were present. The upper jaw was edentulous with inflammation and necrosis of the gums; a black line was present at the gingivodental margins of the gums of the lower jaw. The tongue and mouth were inflamed and contained necrotic and exudative zones. The lungs were clear. The heart appeared normal. The blood pressure was 150 mm. Hg systolic and 70 mm. diastolic. The abdomen was diffusely tender. The liver was palpable 1 cm. below the right costal margin and had a smooth, non-tender edge. The labia majora and minora as well as the vagina were swollen, red, covered with exudate and focally necrotic. The urethral meatus was identified with difficulty.

Examination of the blood revealed 8.5 Gm. of hemoglobin, 20,500 white blood cells with 98 per cent polymorphonuclear leukocytes, 21 per cent of the leukocytes were non-segmented. Urine (4 cc.) were obtained by catheter and contained 4 plus albumin, many red blood

cells, 10 to 15 white blood cells, many epithelial cells and rare granular casts.

Chemical examination of the blood revealed a carbon dioxide content of 26 volumes per cent; non-protein nitrogen 150 mg. per cent; treatment with the artificial kidney was started and was continued for six hours. Heparin (100 mg.) was given into the vein and another 100 mg. was introduced into the apparatus at the onset of treatment. Four hours later 50 mg.

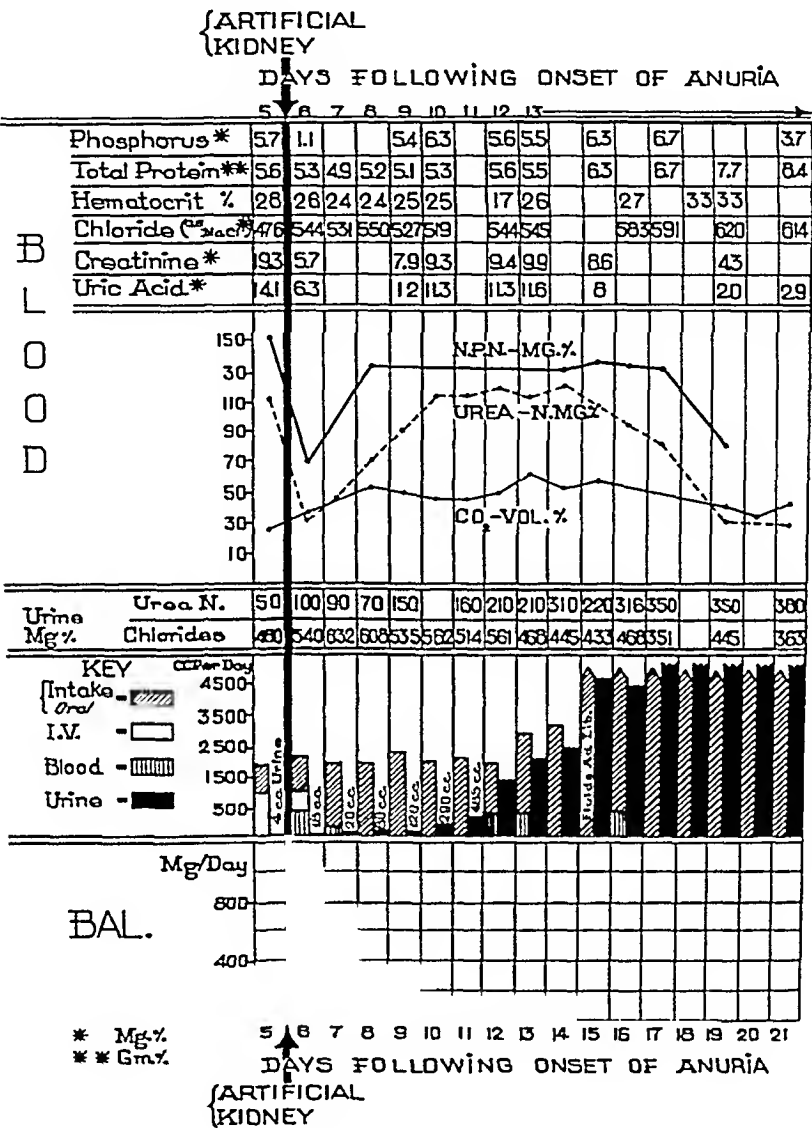


FIG. 3. Case 1. Course in hospital prior to and following the use of the artificial kidney.

urea nitrogen 110 mg. per cent; other significant chemical data are included in Figure 3.

The patient was given 5 per cent glucose in normal saline intravenously to replace fluids lost in vomitus and stool. One hundred seventy-five mg. 2,3 dimercaptopropanol (BAL) was given intramuscularly at regular intervals as indicated in Figure 3. She was also given 25,000 units of penicillin every three hours to combat infection. At 11 p.m. on the day of admission was again administered intravenously. This dosage sufficed to maintain the clotting time of the blood (Lee and White) from one to four hours during the treatment. All observers agreed that she improved markedly during this time. She became less restless, better oriented and was able to request and retain oral fluids. The response of the blood to dialysis and the amounts of each constituent removed from the blood and found in the bath fluid are indicated in Table 1.

There was evidence of slight hemodilution as manifested by the fall in hematocrit and serum protein level after treatment. There was a precipitous drop in blood non-protein nitrogen, urea nitrogen, phosphorus, creatinine and uric acid. The serum sodium levels were 122.0

chromogen level at the end of six hours was 84 mg. per cent. The carbon dioxide content of the blood was not appreciably altered during treatment and remained at 26 volumes per cent. The 100 L. of bath fluid following dialysis contained 24 Gm. of urea nitrogen, 6.7 Gm. of uric

TABLE I

CHEMICAL ANALYSES OF THE BLOOD DURING TREATMENT WITH THE ARTIFICIAL KIDNEY

CASE I. Upper chart: Chemical analysis of blood entering the artificial kidney from the radial artery (A) and leaving the artificial kidney (B) to re-enter the general circulation via the brachial vein. Serial determinations were made at hourly intervals. Note the decrease in dialyzing efficiency of the kidney following the accumulation of retention products in the bath fluid. The efficiency again rose following change in bath water at the end of four hours. The total protein did not vary appreciably.

Lower chart: Chemical contents of bath fluid following six hours of dialysis. Bath water was completely replaced after four hours of dialysis. As above, values are expressed per 100 cc. of solution. The bath contains 100 L. of fluid as indicated in the text.

	Urea Nitrogen (mg. %)	Uric Acid (mg. %)	Creatinine (mg. %)	Phosphorus (mg. %)	Total Protein (Gm. %)	Icterus Index	Hemato-crit
Control*	100	14.1	19.3	5.7	5.6	3	28
1 hour { A †	116	13.4	14.1	6.0	5.3	4	29
{ B ‡	26	8.5	6.2	4.3	5.5	4	29
2 hours { A	86	12.9	15.5	4.4	5.0	9	29
{ B	36	8.2	7.9	2.0	5.3	7	
3 hours { A	68	10.7	13.5	2.3	5.6	12	
{ B	40	7.2	7.1	1.2	5.3	12	
4 hours { A	50	8.1	11.0	1.4	5.6	13	26
{ B	36	5.7	7.1	1.1	5.1	13	
5 hours { A §	48	9.6	9.6	1.6	5.3	14	25
{ B	14	3.7	4.5	0.9	5.5	14	
6 hours A	30	6.9	5.7	1.5	5.3	14	26

Contents of Bath Fluid (mg. %)

	Urea Nitrogen	Uric Acid	Creatinine	Phosphorus	Total Protein
Initial four hours §	19	3.6	7.3	0.6	3.6
Final two hours	5	3.1	2.4	0.4	2.9
Total	24	6.7	9.7	1.0	6.5

* One-half hour before start of treatment with artificial kidney.

† Blood sample from radial artery en route to machine.

‡ Blood sample from machine following dialysis en route to brachial vein.

§ Bath fluid was completely replaced by fresh solution after four hours.

mEq./L. before treatment and 132.4 mEq./L. after treatment. The serum chloride (as sodium chloride) rose from 94 mEq./L. before treatment to 100 mEq./L. at the end of treatment. Slight hemolysis was manifested by yellow discoloration of the serum and a progressive rise in icterus index from 3 to 13 during the six-hour period. Serum hemo-

acid, 9.7 Gm. of creatinine, 1.0 Gm. of phosphorus and 6.5 Gm. of protein. No mercury could be identified in the bath fluid.²⁰ At the close of treatment with the artificial kidney she was given 300 cc. of 5 per cent sodium bicarbonate to combat acidosis.

Subsequent to treatment with the artificial kidney she was given a high-carbohydrate,

high-fat diet containing no protein. After the first two days she was able to retain the equivalent of at least 1,500 calories per day. Fluids were administered almost exclusively by mouth except for occasional whole blood transfusions as indicated in Figure 3. The amount of fluid consisted of 1,000 cc. per twenty-four hours to compensate for insensible water loss plus the equivalent of the fluid lost by diarrhea and vomiting. The amounts of oral sodium chloride and sodium bicarbonate were varied according to the serum chloride and carbon dioxide content but averaged approximately 4 Gm. of sodium chloride and 16 Gm. of sodium bicarbonate per day.

Diarrhea and vomiting persisted for four days following use of the artificial kidney, gradually decreasing in frequency and content. The ulceronecrotic lesions of the buccal and vaginal mucous membranes responded sluggishly to local applications but gradually improved. On the eighth and ninth days following onset of anuria, pretibial and facial edema appeared but spontaneously subsided. On the eighth day after use of the artificial kidney she appeared more rational, with only occasional disorientation and periods of delusion and paranoia. She responded well to questioning and appeared to be convalescing well.

The urinary output increased gradually until the twelfth day following onset of anuria when the output approximated the intake. The urine was voided through a markedly inflamed area and the significance of albumin, red cells and white cells was difficult to determine. Granular casts were carefully sought but only rarely found during the period of observation. The urea nitrogen of the urine rose slowly to a maximum of 380 mg. per cent. The urinary chlorides varied from 351 to 632 mg. per cent (measured as sodium chloride). The specific gravity of the urine did not fall below 1.010 or rise above 1.012. On the fifteenth day following onset of anuria she was allowed fluids *ad libitum* and following the seventeenth day the urinary output constantly exceeded 4,500 cc. per twenty-four hours.

Following treatment with the artificial kidney, the blood non-protein nitrogen and urea nitrogen showed a parallel rise. Serum phosphorus, uric acid and creatinine also rose. The serum chlorides and carbon dioxide content were readily controlled by oral administration of sodium chloride and sodium bicarbonate.

Despite the adequacy of urinary output on the twelfth day following onset of the anuria and subsequent diuresis, the blood urea nitrogen, non-protein nitrogen, creatinine, uric acid and phosphorus only gradually returned to normal.

On the twelfth day following treatment with the artificial kidney the patient began to menstruate. She became hypomanic. The agitation failed to subside, paranoia supervened and delusions and hallucinations were expressed which centered around the events which had initiated the present illness. It became necessary to send the patient elsewhere for psychiatric care. A later report by Dr. R. E. Blaisdell, Rockland State Hospital, Orangeburg, N. Y., indicated that analyses made on March 5th showed the following: urea nitrogen, 13 mg. per cent; creatinine, 1.4 mg. per cent; uric acid, 2 mg. per cent; non-protein nitrogen, 30 mg. per cent. The specific gravity of the urine was 1.013.

Comment. In this instance the self-administered dose of mercury bichloride was especially large. The 2.5 Gm. instilled into the vagina remained *in situ* until completely absorbed. The subsequent symptoms were those of severe systemic mercurialism.

The patient was admitted to the Mount Sinai Hospital on the fifth day of anuria. The clinical manifestations were those of uremia, acidosis and dehydration. All observers agreed that the patient was virtually moribund. She was given BAL and intravenous alkali prior to the artificial kidney. She was treated with the artificial kidney on the day of admission. During the process of dialysis she appeared to improve and become more rational. The artificial kidney functioned well mechanically. There was a precipitous fall in non-protein nitrogen, urea nitrogen, creatinine, uric acid, and phosphorus as indicated in Table 1. Calcium gluconate (1 Gm.) was administered intravenously at hourly intervals to replace the calcium lost by dialysis. The bath fluid at the end of the treatment was found to contain a total of 24 Gm. of urea nitrogen, 6.7 Gm. of uric acid, 9.7 Gm. of creatinine and 1 Gm. of phosphorus. Protein (6.5 Gm.) were also present in the bath indicating slight permeability of the

membrane. The level of serum proteins was not appreciably altered. The hematocrit decreased slightly. Slight hemolysis was noted as the icterus index increased from 3 to 14, serum bilirubin from 0.2 and 0.5 mg. per cent and the van den Bergh reaction became delayed positive.

The subsequent management of the patient corresponded to that previously outlined.² An attempt was made to increase gradually the intake of a high-carbohydrate, high-fat, protein-free diet in order to supply adequate caloric intake. Electrolyte balance was maintained by oral administration of sodium chloride and sodium bicarbonate.

Adequate urinary output was established on the twelfth day after the onset of anuria and seven days following use of the artificial kidney. Figure 3 illustrates the gradual fall in the serum levels of non-protein and urea nitrogen despite diuresis due to the lack of renal concentrating capacity. During convalescence urea nitrogen concentration of the urine remained low. The urine chloride concentration was relatively constant—an indication of the inability of the tubules to vary the excretion of chloride in accord with the body need. The leukocytosis gradually receded and fewer transfusions were required to maintain the hemoglobin level.

Identification in this instance of any specific agent as responsible for restitution of kidney function is not possible. BAL administered more than three hours after the application of mercury is reported to have little effect on the outcome.²¹ In this patient it was started on the fifth day of anuria. We have stressed previously that patients with mercury intoxication or any type of lower nephron nephrosis²² may survive the toxic injury if electrolyte balance is maintained and circulatory embarrassment is avoided. The previously recommended measures² were again used in this case and unquestionably contributed materially to her recovery. During treatment with the artificial kidney all were impressed by the apparent innocuousness of the procedure and the clinical as well as chem-

ical improvement manifested by the patient. It is believed that the artificial kidney may have provided additional time for spontaneous improvement to occur.

CASE II. W. M., a thirty year old male who on April 1, 1948, was exposed in a small closed room to intense carbon tetrachloride fumes for five hours. After leaving the room he felt "drunk." The next day generalized muscular aches, anorexia, oliguria, and bilateral costovertebral angle pain appeared. These symptoms progressed and on April 4th he was hospitalized elsewhere. Examination revealed him to be acutely ill with slight scleral icterus. The temperature was 100°F., pulse 72 per minute and respirations 20 per minute. The blood pressure was 144 mm. Hg systolic and 90 diastolic. Tenderness was present in the mid-epigastrium and in both costovertebral angles. There was moderate anemia (10.5 Gm.). The urine contained moderate amounts of albumin and microscopic examination revealed many red blood cells. There was no choluria; the urinary urobilinogen was normal. The icterus index was 19. The cephalin flocculation test was strongly positive. The serum cholesterol was 118 mg. per cent with 63 per cent esters. Oliguria persisted, anuria ensued on April 8th. The blood urea continued to rise. Parenteral fluids were cautiously administered to replace fluids lost by vomiting and insensible loss. Methionine, choline and parenteral vitamins were given to combat hepatic injury. On April 9th pulmonary and systemic hypertension appeared, and following phlebotomy he was transferred to the Mount Sinai Hospital.

On admission he was found to be acutely ill, with a urinous odor to his breath. The sensorium was cloudy. The blood pressure was 148 mm. Hg systolic and 90 diastolic. Bilateral subconjunctival hemorrhages were present and were ascribed to repeated episodes of vomiting. Clotted blood was present in the nares. The heart and lungs were normal. The abdominal viscera were not palpable. The hemoglobin was 10.5 Gm. There were 10,450 white blood cells with a shift to the left of the leukocyte series. There were 290,000 platelets. The blood non-protein nitrogen was 170 mg. per cent; urea nitrogen 108 mg. per cent; serum chlorides (as sodium chloride) 423 mg. per cent; carbon dioxide content 59 volumes per cent and hematocrit 39 per cent. Clotting time, bleeding

TABLE II

CASE II Course of patient with carbon tetrachloride intoxication prior to and following onset of diuresis. Artificial kidney was used on tenth and sixteenth days of illness. Frequent whole blood transfusions were administered following onset of diuresis to overcome the anemia and neutralize the prothrombin deficiency.

Day of illness	Urine		Blood		Hemato- crit (%)	Blood		Weight (pounds)	Blood Pres- sure (mm. Hg)	Vomi- tus (cc./ 24 hr.)	
	Urea Nitro- gen (mg. %)	Chlo- rides (NaCl) (mg. %)	Urea Nitro- gen (mg. %)	Crea- tinine (mg. %)		Hemo- globin (Gm. %)	Xantho- proteins (units)				
4	100							136.5	144/90	0	Hospitalized elsewhere; hematemesis; ic- terus; oliguria
5	100		63	18	41.4			..	150/70	125	Epistaxis; rational and alert; anorexia
6	100		65		43.3			..	140/94	350	Drowsy; blood-tinged emeta
7	70		65		37.6			..	140/90	475	Loin pain
8	0		95		59	10.5		..	142/88	825	Phlebotomy
9	180	117	109	15.2	29	10.5		140.5	170/100	317	Transferred to Mt. Sinai Hospital; uremic; cloudy sensorium; prothrombin deficiency
10	120	59	108		28	10.5	110	140.0	160/100	960	Artificial kidney
11	72	389	69		27	8.5	80	..	150/80	1210	Comfortable; alert
12	90	304	71	16.5	55	8.5	..	136.5	158/86	400	
13	72	280	73	18.6	62	8.0	86	138	130/80	1055	Drowsy
14	96	236	86		53	10.0	104	138.5	144/90	1000	
15	119	386	92	18.1	62	9.8	116	136	148/100	1769	Persistent vomiting; drowsy; irritable
16	200	351	98		54	9.0	125	..	130/90	135	Artificial kidney
17	270	397	53		62	7.2	101	..	130/80	760	Oozing from wound sites; fresh whole blood
18	604	316			129	160/90	950	Comfortable; alert
19	1193	293	89		52	8	129	125	140/80	1625	
20	2278	360	98		66	6.0	116	124	150/90	400	Cellulitis of foot
21	2527	360	98			7.3		123	150/88	0	
22	2653	520	91		41	9.2	66	..	150/98	0	
23	2652	570	105		33	10.0		..	160/100	235	
24	2249	660	104	9.8	52			..	130/88	1060	
25	2228	750	93		515			..	128/88	370	Cellulitis resolving
26	2370	720	105		36	11.0		..	152/88	0	
27	2378	710	48		61	..	31	116	122/88	200	Eating well
28	2202	690	40		66	9.0		117	140/90	0	
29	2465	640	42			10.2		117	135/90	0	Out of bed
30	3705	198	38		590	10.6		119	130/80	0	
31	3260	222	32		579	10.8	..	120	130/80	0	
32	2840	270	28		602	11.0	..	120	126/80	0	
33	2160				626	12.2	..	122	122/80	0	

time, clot retraction and tourniquet test were all normal. The cephalin flocculation and thymol turbidity tests were negative. The icterus index was 2. The prothrombin activity was found to range from 17 per cent to 50 per cent of normal.

In the twenty-four hours following admission

effective in removing retention products from the blood (Table III), diuresis did not ensue and uremia again gradually became manifest. On April 16th he was again treated with the artificial kidney. (Table IV.) The same amount of heparin was administered as on the previous

TABLE III

CHEMICAL ANALYSES OF THE BLOOD DURING TREATMENT WITH THE ARTIFICIAL KIDNEY

CASE II: Chemical analysis of blood and bath fluid during initial treatment with artificial kidney. Bath fluid completely changed after four hours. Phenols were found in all bath fluids.

	Urea Nitrogen (mg. %)	Uric Acid (mg. %)	Creatinine (mg. %)	Phosphorus (mg. %)	Total Protein (Gm. %)	Icterus Index	Hemato- crit
0 hours	108	11.3	15.2	4.1	6.5	3	28
2 hours { A	80	11.5	28.3	4.0	6.3	3	30
{ B	30	8.0	15.0	3.1	6.7	3	
4 hours { A	76	10.0	25.2	2.9	6.1	3	28
{ B	34	7.6	16.4	2.6	6.0	3	
6 hours { A	54	8.3	23.2	3.1	5.7	3	26
{ B	14	5.5	10.3	1.8	6.7	3	

Contents of Bath Fluid (mg. %)

	Urea Nitrogen	Uric Acid	Creatinine	Phosphorus	Total Protein
2 hours.....	18	2.3	6.2	1.4	2.2
4 hours.....	27	2.8	8.5	3.1	4.3
6 hours.....	7	1.0	3.9	1.0	4.0
Total.....	34	3.8	12.4	4.1	8.3

180 cc. of bloody urine were obtained by catheter. The urine was acid (pH 5); the specific gravity was 1.016. Moderate amounts of albumin were present and many red blood cells and few white blood cells were found on microscopic examination.

Vitamin K (4.8 mg. hykinone daily) failed to return the prothrombin time to normal. He was treated for six hours on April 10th with the artificial kidney. Heparin (100 mg.) was injected into the venous cannula; 100 mg. were injected into the arterial cannula leading to the machine; 50 mg. were administered after two hours to maintain the prolonged coagulation time. He remained comfortable during the period of dialysis; the blood pressure did not vary significantly. There was no evidence of hemorrhage.

His course following the initial treatment is outlined in Table II. Although dialysis was

occasional. However, oozing of blood appeared from abraded areas about the mouth and nose and after six hours the dialysis was terminated. Toluidine blue, 3 mg./Kg., and whole blood were administered to neutralize the heparin. The oozing persisted (even though the coagulation time of the blood rapidly returned to normal) and was ascribed to the prothrombin deficiency.

The subsequent course of the patient was uneventful except for persistent vomiting which slowly subsided. Following the second treatment with the artificial kidney, there was a progressive increase in the daily volume of urine. (Table II.) By the twentieth day of illness more than 2,000 cc. of urine were being voided daily. The urine which had been grossly bloody on admission became free of red blood cells; casts were rare at all times. Albuminuria diminished; the pH of the urine became less fixed. The con-

centration of urea nitrogen in the urine gradually rose and the selective elimination of chlorides reappeared. The specific gravity of the urine varied slightly from 1.010. The azotemia slowly subsided as restoration of kidney tubular function occurred.

taneously exposed to lesser concentrations of the vapors, was admitted elsewhere because of hematemesis and jaundice. He was discharged after ten days, free of symptoms, with no evidence of renal damage.

TABLE IV

CHEMICAL ANALYSES OF THE BLOOD DURING TREATMENT WITH THE ARTIFICIAL KIDNEY

CASE II: Chemical analyses of blood and bath fluid during second treatment with artificial kidney. Bath fluid changed after four hours. Phenols were present in the bath fluid after dialysis. The xanthoprotein concentration of the blood fell following dialysis.

	Urea Nitrogen (mg. %)	Uric Acid (mg. %)	Creatinine (mg. %)	Phosphorus (mg. %)	Total Protein (Gm. %)	Icterus Index	Hemato- crit	CO ₂ Content (vol. %)
0 hour	85	5.6	27.2	7.5	7.2	3	30	
2 hours { A	71	4.3	26.4	7.1	7.4	3	30	35.5
{ B	24	2.3	16.1	5.0	7.4	3	..	30.0
4 hours { A	32	3.2	22.9	4.0	7.4	3	27	39.4
{ B	13	1.9	11.1	3.0	7.0	3	..	32.6
6 hours { A	35	2.5	19.8	3.0	7.4	3	25	40.9
{ B	19	1.8	12.0	2.5	7.0	3	..	31.7

Contents of Bath Fluid (mg. %)

	Urea Nitrogen	Uric Acid	Creatinine	Phosphorus	Total Protein	CO ₂ Content
2 hours . . .	10	1.2	4.8	0.8	0	54.6
3 hours . . .	23	1.6	8.9	1.7	10	50.9
6 hours . . .	18	1.4	7.8	1.0	12	
Total	41	3.0	16.7	2.7	22	

The patient was remarkably comfortable during the entire period of renal insufficiency. Daily records were kept of fluid loss and cautious replacement served to maintain hydration as well as adequate carbon dioxide and chloride contents of the serum. Whole blood and washed red blood cells were used to combat anemia.

Comment. In this patient the nephrotoxic effects of carbon tetrachloride poisoning dominated the clinical picture. Hepatic injury was manifested by the transient icterus, bleeding due to persistently reduced prothrombin activity and abnormal retention of bromsulfalein in the blood; there was also no increase in prothrombin activity following administration of vitamin K. The patient's co-worker, who had been simul-

The patient was treated with the artificial kidney on the tenth and sixteenth days of illness. Both treatments were effective in eliminating retention products from the blood stream. (Tables III and IV.) The serum chlorides rose following the dialysis; carbon dioxide escaped from the blood during its exposure to the bath fluid. Phenols and xanthoproteins passed from the blood into the bath fluid.

The clinical course of the patient was characterized by freedom from urenic manifestations despite the long period of renal insufficiency. Following the onset of polyuria on the twentieth day of illness, azotemia gradually subsided. (Table II.) Recovery of normal tubular function evolved

slowly. It is believed that in this instance the artificial kidney served as a temporizing measure which potentiated spontaneous restoration of kidney structure and function.

CASE III. B. C., a sixty-three year old white man had had prostatism since 1933. Prior to hospitalization the urine was normal on repeated analyses. The blood pressure regularly averaged approximately 120 mm. Hg systolic and 80 diastolic. On May 1, 1947, cystoscopy was performed and the patient was admitted to another hospital in preparation for prostatectomy. On May 2 a Foley catheter was introduced for drainage and lavage. Twelve hours later the patient withdrew the catheter because of local irritation. His temperature rapidly rose to 106.8°F. He was given 1 Gm. of sulfadiazine by mouth and one intramuscular injection of penicillin. However, in the next twelve hours he voided only 100 cc. of bloody urine; sulfadiazine was discontinued. Fluids were given parenterally in large quantities; pulmonary edema ensued and was treated by phlebotomy and digitalization. Anuria persisted from May 2nd to May 7th when he was transferred to the Mount Sinai Hospital. The blood urea nitrogen had now risen to 102 mg. per cent, the creatinine to 7 mg. per cent; the carbon dioxide combining power was 32 volumes per cent. There was moderate anemia, leukocytosis and shift to the left of the white cell series.

On physical examination the patient was seen to be a well developed, obese, semistuporous male. He was restless, with spasmodic body twitchings and hyperirritability to minimal stimuli. The tongue was dry. Excoriations were present about the mouth and face. The veins of the neck were distended. The chest was emphysematous and moist rales were audible in both pulmonary bases. The respiratory rate was 28 per minute. The heart appeared enlarged to the left by percussion. The rhythm was regular with a rate of 100 per minute. The blood pressure was 105 mm. Hg systolic and 60 diastolic. The liver was enlarged 3 cm. below the right costal margin. Hepatojugular reflux was present. Moderate anasarca was present. The prostate was smooth, uniformly enlarged and approximately twice the normal size. A Foley catheter was in place.

On admission 30 cc. of one-sixth molar sodium lactate solution was given intravenously. A scout film of the abdomen revealed no evidence

of calculi. The Foley catheter was removed. Cystoscopy on May 7th revealed that the bladder was diffusely inflamed, the mucosa being lined with shreds of muco-pus. The ureteral orifices could be seen but catheters could only be passed for a distance of 0.5 cm. on each side. The lateral lobes of the prostate were found to be enlarged and met in the midline. The Foley catheter was replaced.

The repeated manipulations including cystoscopy rendered inadvisable the heparinization required in use of the artificial kidney. Peritoneal lavage was deferred because of the marked degree of debility, abdominal distention and ascites. The diet was restricted to fats and carbohydrates. Oral fluids were supplemented by approximately 300 cc. of one-sixth molar lactate per day. However, the patient continued to deteriorate. Coma and uremic frost appeared on May 11th. All other available measures having been exhausted, on May 11th treatment with the artificial kidney was started and continued for four hours. Calcium gluconate, 10 cc. of 10 per cent solution, was given intravenously at hourly intervals. During the treatment the blood pressure ranged from 130 to 170 mm. Hg systolic and 60 to 70 mm. diastolic. A febrile reaction to 104°F. occurred after one hour and was ascribed to the heparin and pyrogens in the tubing. The patient roused somewhat and the chest was free of rales after two hours. He was able to ask for fluid. The twitchings gradually diminished. However, the excoriations about the face began to ooze blood and at 1 A.M. on May 12th the treatment was stopped. A total of 820 mg. of heparin had been given intravenously during the treatment. Blood samples drawn from the patient failed to clot during the four hours of treatment. When the oozing of blood started, 500 cc. of fresh whole blood was slowly administered through the side circulation (Fig. 2) of the artificial kidney. The patient left the treatment room not appreciably altered clinically from the time of the onset of therapy.

At 6:45 A.M., 275 cc. of urine was found in the drainage bottle. The bleeding had stopped. The clotting time had reverted to normal. The blood pressure was 154 systolic and 68 diastolic. However, the patient's coma deepened and he expired at 7:45 A.M.

Autopsy revealed acute hemorrhagic bronchopneumonia involving the right upper, middle and left upper lobes. Acute tracheobronchitis

and pulmonary edema were present. Small hemorrhagic foci were found in the bladder, ureters, pelvis, kidneys, stomach, vocal cords, right epididymis, and around skin needle-puncture sites. Fibro-adenomatous hyperplasia of the prostate was marked.

The kidneys were enlarged, weighing 485 Gm. together. Fine punctate hemorrhages studded the surface. The surfaces of section were hyperemic; the corticomedullary demarcation was distinct. The glomeruli were visible as pale dots against an edematous background of cortex. The medulla was congested. Microscopic examination revealed congested and ischemic glomeruli frequently containing albuminous debris in Bowman's space. The proximal convoluted tubules showed mild degenerative changes. The distal convoluted tubules and collecting tubules were severely inflamed and contained zones of atrophy, necrosis and regeneration. The lumina contained eosinophilic, homogeneous and granular casts. The interstitium was focally infiltrated with chronic inflammatory cells. The intertubular capillaries were markedly congested. Several veins in the cortex were thrombosed.

The brain revealed discrete foci of hemorrhage and encephalomalacia, most marked on the lateral surface of the right temporal lobe. Microscopically, there was evidence of marked stasis and increased vascular permeability.

Comment. This was our first experience with the artificial kidney. The anuria was ascribed to cystoscopy, ureteral catheterization and sulfadiazine. The artificial kidney was used only after all hope for recovery had been exhausted. Urine (275 cc.) was voided in the six hours prior to death. At the present time we realize that treatment should not be deferred until irreversible changes have occurred. Moreover, if treatment with the artificial kidney is contemplated, surgical manipulation and creation of potential sites of bleeding should be avoided. The excoriations about the face and mouth were presumably due to pressure of oxygen masks and nasal catheters. These sites bled following heparinization. At autopsy small hemorrhages were found in the kidneys, bladder, pelvis, ureters, stomach and vocal cords. These areas had been the site of manipulation by either catheters

or Levine tubes. A hemorrhagic bronchopneumonia was present. Small foci of hemorrhage were found in the brain. It was recognized that the doses of heparin recommended by Kolff were far in excess of the amount required to prevent coagulation

TABLE V
BLOOD UREA NITROGEN AND SERUM CHLORIDES DURING TREATMENT WITH ARTIFICIAL KIDNEY

CASE III: Chemical analyses of the blood during treatment with the artificial kidney. A, indicates the blood as it entered the machine from the radial artery; B, as it left the machine following dialysis prior to entry into a brachial vein. The water in bath at the end of four hours contained 27 Gm. of urea nitrogen.

	Urea Nitrogen (mg. %)	Chlorides (mg. %)	CO ₂ Content (vol. %)
1 1/4 hours { A.	244	515	38.2
B.	13	655	35.1
2 1/2 hours { A.	232	538	37.4
B.	27	644	24.2
3 3/4 hours { A.	226	550	34.4
B.	13	642	21.5

during the passage of blood through the artificial kidney. This discrepancy between the recommended and required dose of heparin is perhaps explained by the lower potency of the heparin available to Kolff.

Urea nitrogen (27 Gm.) was removed from the blood in four hours and marked differences were noted in the urea nitrogen content of blood entering and leaving the machine. (Table v.) The carbon dioxide content of the patient's serum fell slightly during treatment. The carbon dioxide content of the blood leaving the artificial kidney was much lower than that of the blood entering the machine. This effect was believed due to the escape of carbon dioxide in the process of dialysis. Unfortunately carbon dioxide combining power of the serum was not determined. The carbon dioxide content of the original bath fluid was 53 volumes per cent; the final content was 49.4 volumes per cent. Serum chlorides increased gradually to a normal level. The bath fluid contained 749 mg. per cent of chlorides (as sodium chloride) at the end

of the run; the original bath fluid had contained 674 mg. per cent. This alteration in bath fluid can be explained by a decrease in volume due to evaporation.

CASE IV. E. G., a thirty-three year old woman in June, 1947 inserted two tablets of potassium permanganate into the vagina in order to induce an abortion. On July 5th, her menses failing to appear, she inserted two additional tablets. On the following day profuse vaginal bleeding began; she had shaking chills and a fever of 106°F. A physician administered one injection of 100,000 units of penicillin subcutaneously. In the subsequent twelve hours the patient also ingested 5 Gm. of sulfadiazine and 1½ Gm. of sodium bicarbonate. The chills and fever persisted and she was admitted to another hospital on July 7th. Physical examination revealed scleral icterus, slight tenderness in the right upper quadrant and vaginal bleeding. The hemogram revealed 3.75 million red blood cells, 22,500 white blood cells with 89 per cent polymorphonuclear leukocytes. Urine obtained by catheter contained bile, many red blood cells and a trace of albumin. The icterus and choluria disappeared several days after admission. On July 8th membranes which protruded from the cervical os were removed. She was treated with penicillin intramuscularly for the septic abortion and the temperature rapidly returned to normal. Oliguria was noted in the twenty-four hours following admission. On July 10th her blood urea nitrogen was found to be 150 mg. per cent.

On July 12, 1947, cystoscopy was performed. A few drops of clear urine were obtained from each ureter. The catheters were left in place for forty-eight hours but no urine was obtained. The patient became drowsy, nauseated and extremely thirsty. She was treated with intravenous sodium chloride, sodium lactate, Ringer's solution, sodium bicarbonate and a high colonic slow drip of 10 per cent magnesium sulfate. However, she failed to respond to these measures and on July 18th, following a transfusion of 250 cc. of whole blood, she was transferred to the Mount Sinai Hospital. At this time her blood urea nitrogen was 245 mg. per cent, creatinine 8.5 mg. per cent and the carbon dioxide combining power was 17 volumes per cent. Icterus index was 11, the van den Bergh test was negative, total proteins were 5.1 Gm. per cent (with a normal albumin-globulin ratio)

and cholesterol was 124 mg. per cent (with 55 per cent esters).

Physical examination on July 18th revealed the presence of dyspnea, orthopnea, tachypnea and Kussmaul breathing. Twitchings were conspicuous. The temperature was 99.6°F.; pulse 120 per minute; respirations 40 per minute. The blood pressure was 140 mm. Hg systolic and 70 diastolic. There was moderate edema of the abdominal wall and back. Fine and coarse moist rales were heard at both lung bases. The abdomen was somewhat distended. Shifting dullness was present. No viscera were palpable in the abdomen. The remainder of the examination was within normal limits.

Laboratory studies on admission revealed a hemoglobin of 5.4 Gm.; 1.72 million red blood cells; 17,500 white blood cells, of which 87 per cent were segmented polymorphonuclear leukocytes, 4 per cent non-segmented and 6 per cent lymphocytes. Urine, 30 cc., were voided in the initial twenty-four hours following admission. The specific gravity was 1.010. The urine was straw-colored, cloudy, the pH was 7.0. It contained moderate amounts of albumin and many white blood cells and red blood cells on microscopic examination. The urinary chlorides were 621 mg. per cent; the urea nitrogen of urine 310 mg. per cent. The blood urea nitrogen was 145, uric acid 18.7 and creatinine 15.9 mg. per cent. The carbon dioxide content was 12.1 volumes per cent. The primary cause of the oliguria was not clear. Administration of sulfadiazine and cystoscopy seemed to be possible aggravating factors. The patient was given supportive therapy with digitalis, small transfusions of whole blood and oral and intravenous sodium bicarbonate. A necrotic placental mass was removed a few hours after admission.

On July 19th, although the patient appeared comatose and virtually moribund, the artificial kidney was applied. Heparin, 450 mg., was administered slowly through the venous cannula in divided doses. An hour after the cannula had been introduced a chill occurred and the temperature rose to 103°F.; this gradually subsided. Throughout the run there was no sign of improvement. At the end of one one-half hours the blood pressure gradually began to fall. The run was immediately terminated and 750 cc. of whole blood was given through the collateral inlet of the artificial kidney. Ten minutes after the treatment was terminated she again had rigors and twitchings which did

not respond to intravenous calcium gluconate. She remained in a coma and in peripheral collapse. The blood pressure was not measurable and the ventricular rate was 160 per minute with a tie-tac rhythm. No focal neurologic signs were obtained. The next morning she was unresponsive but had voided 2 ounces of urine. The lungs were clear. The clotting time was normal. The blood urea nitrogen was 195 mg. per cent, uric acid 19.1 mg. per cent, chlorides 580 mg. per cent, total protein 6.9 Gm. per cent and carbon dioxide content 10.7 volumes per cent. In the twenty-four hours following dialysis she voided 100 cc. of grossly bloody urine. Her blood pressure gradually returned to 110 systolic and 40 diastolic. Her downhill course continued and she expired on July 21st, fourteen days after oliguria was first noted.

Postmortem examination revealed no evidence of hemorrhage. The kidneys revealed the gross picture of lower nephron nephrosis. Their combined weight was 680 Gm. They appeared firm and tense. The exposed surface was dark gray and stippled. The cut surface revealed indistinct corticomedullary demarcation. The cortex was pale and edematous; the medulla revealed exaggerated black-gray rays converging in each papilla. The brain was edematous. Microscopic examination of the kidneys confirmed the gross impression.²²

Comment. The patient was transferred to this hospital in terminal uremia, severe heart failure and marked acidosis. Urine (30 cc.) were voided prior to her treatment with the artificial kidney and 60 cc. were voided following treatment. The chills and fever shortly after the start of dialysis were believed to be due to the heparin or pyrogens in the tubing despite scrupulous preparation. The fall in blood pressure made continuation of the treatment impossible since circulation through the machine could not be continued. At the end of the two-hour treatment with the artificial kidney 14 Gm. of urea nitrogen were found in the bath fluid. Other determinations were not attempted due to the unsatisfactory condition of the patient.

CASE V. J. W., a fifty-six year old white male, was admitted to the hospital on July 3, 1947, because of rectal bleeding which occurred with

each bowel movement. Control of the anal sphincter had been lost seventeen years prior to admission following surgery for a rectal abscess. Slight anorexia and a 12-pound weight loss had been noted during the six months prior to admission. The remainder of the patient's personal and family history was non-contributory.

Physical examination revealed a well developed, well nourished, chronically ill man. Temperature was 99°F.; pulse, 75; respirations, 14. The blood pressure was 145 systolic and 70 diastolic mm. Hg. The significant physical abnormalities were confined to the rectum which revealed the scars of previous surgical operations, a lax sphincter tone and a sessile fungating mass on the anterior and right lateral walls of the rectum.

Hemoglobin on admission was 13.0 Gm. The blood count and urinalysis were normal. The blood group was O (Landsteiner).

On July 7, 1947, an abdominoperineal resection was performed for adenocarcinoma of the rectum. The extension of the carcinoma into adjacent structures rendered its removal difficult. Bleeding was profuse and the blood pressure fell to 55 systolic and 30 diastolic. Despite administration of 2,000 cc. of whole blood the blood pressure remained at 75 systolic and 50 diastolic. A chill occurred following administration of the third 500 cc. of whole blood. Investigation revealed that 500 cc. of group A (Landsteiner) blood had been given. Following the subsequent administration of 2,500 cc. of whole blood, 500 cc. of saline and 600 cc. of one-sixth molar sodium lactate solution intravenously, the blood pressure gradually rose to 124 systolic and 69 diastolic. The marked fall in blood pressure had persisted for approximately eight hours.

The subsequent course of the patient, urinary output, blood and urine examinations are illustrated in Table VI. On July 8th, the morning following the operation, the blood pressure was 130 systolic and 70 diastolic. The patient was drowsy, responded poorly but was coherent. The total volume of intravenous and oral fluid was limited to a slow replacement of the amount obtained by Wangenstein suction plus 1,000 cc. for insensible loss. The choice of isotonic sodium chloride, 5 per cent glucose or one-sixth molar lactate was determined by the carbon dioxide and chloride content of the blood. Only 15 cc. bloody urine were voided during the twelve hours following operation. Successive specimens

of urine were found to contain large amounts of albumin, many epithelial cells, 6 to 10 red blood cells and a few to many white blood cells per high power field. The specific gravity of casual specimens ranged from 1.014 to 1.019. The hemoglobin was 10.4 Gm. On July 10th the

TABLE VI

CASE V: Course prior to and following treatment with the artificial kidney.

July	Urine		Blood			Blood Pressure
	Vol./ 24 hr.	Urea Nitrogen (mg. %)	Urea Nitrogen (mg. %)	Uric Acid (mg. %)	Carbon Dioxide Content (vol. %)	
5	9	145/70
8	15 cc.	...	33	54.5	55/30
9	47 cc.	50	50	4.6	60.5	130/70
10	60 cc.	72	68	5.9	57.0	136/80
11	80 cc.	125	81	6.6	42.4	136/78
12	80 cc.	150	125	7.5	47.0	136/76
13	250 cc.	...	120	61.0	154/70
14	200 cc.	175	147	9.2	184/84
15	200 cc.	163	183	10.5	51.0	172/84
16	275 cc.	388	142	10.1	37.0	180/80
17*	250 cc.	330	95	11.9	41.0	176/84
18	475 cc.	260	107	14.3	50.0	110/70
19	725 cc.	160/64
						130/70

*Chemical values on July 17th were determined on blood drawn nine hours after artificial kidney was disconnected.

patient was alert and cooperative. Dependent edema and basal pulmonary rales appeared which promptly responded to further fluid restriction and digitalization. On July 13th the colostomy functioned well. On July 15th twitchings appeared and the patient appeared somnolent. Occasional, moist, bilateral, basal rales were heard. On July 16th he could not be roused. Twitching and hypersensitivity to mild stimuli were marked. The lungs were full of coarse, moist rales. All observers agreed that the patient was *in extremis*. It was thought that all other available measures had been exhausted and that the artificial kidney could certainly do no harm.

The patient was treated with the artificial kidney on July 16th for eight hours. Heparin (700 mg.) was given intravenously over the initial two-hour period. Serial studies of the clotting time failed to reveal any evidence of clotting during the eight hours. The blood pressure was well maintained during this entire period. Restlessness and twitchings became less marked and after two hours the patient responded to his name. At the end of the dialysis

the pulmonary edema was no longer present. Following this marked improvement, the patient slowly became semicomatose once more. Perineal oozing of blood was noted after six hours. Whole blood (1,000 cc.) was then administered slowly, by-passing the machine. At the end of the dialysis an estimated 500 cc. of the patient's blood was deliberately left in the machine to prevent overloading of his circulation. One hour after completion of the dialysis the oozing stopped. The details of alterations in the patient's blood and the contents of the bath fluid following dialysis are included in Table VII.

The blood urea nitrogen had risen from 9 mg. per cent on July 7th to 142 mg. per cent on July 16th immediately prior to application of the artificial kidney. After eight hours of dialysis the urea nitrogen level had fallen to 92 mg. per cent. However, the level again rose in the ensuing days. This rise is ascribed to persistent oliguria, impaired concentrating capacity of the kidneys, continued endogenous production of urea nitrogen, and re-equilibration of the dialyzed circulating blood with the tissue fluids. Similarly, in the nine days prior to dialysis the serum creatinine rose from 2.9 mg. per cent to 5.8 mg. per cent. Following dialysis the blood level fell to 4.7 mg. per cent but three days later had again climbed to 11.2 mg. per cent. During the eight hours of treatment the serum chlorides increased slightly. The total proteins were not significantly altered. Slight hemolysis was indicated by the gradual increase in icterus index. Changes in blood constituents during and following dialysis are indicated in Tables II and III. No change in blood volume was demonstrated prior to or after the run (Evans blue).

The morning after treatment, July 17th, the patient was restless and disoriented. There was marked sweating, twitching and cyanosis. The lungs were clear. The blood pressure was 110 systolic and 70 diastolic. On July 18th nuchal rigidity appeared. Lumbar puncture yielded bloody, xanthochromic fluid. No microorganisms were found on smear or culture. Total protein and chlorides were normal. The blood pressure was 160 systolic and 64 diastolic. On July 20th bilateral, constant Babinski reflexes and Cheyne-Stokes respiration were observed and the patient died.

Postmortem examination revealed severe pulmonary edema, congestion and broncho-

pneumonia. Both cardiac ventricles were dilated. Multiple, small focal ecchymoses were found in the renal pelvis and bladder mucosa.

The kidneys grossly presented the picture of hemoglobinuric nephrosis. Microscopic examination revealed normal-appearing glomeruli

had gradually increased to 275 cc. in the twenty-four hours prior to dialysis.

Analytic data obtained during dialysis are given in Table VII. The blood urea nitrogen, creatinine and uric acid fell steadily during dialysis; the concentration

TABLE VII

CHEMICAL ANALYSES OF THE BLOOD DURING TREATMENT WITH ARTIFICIAL KIDNEY

CASE II: Upper chart: Blood chemistries before and after dialysis. The dialysis decreased in efficiency because the bath water was not changed during the entire eight-hour run. Lower chart: Bath water samples taken at two-hour intervals indicate gradual increase of dialyzed products. Total bath fluid is 100 L. Consequently, in eight hours 59 Gm of urea nitrogen, 2.5 Gm. of creatinine and 2.9 Gm. of uric acid had been removed from the blood.

	Urea Nitrogen (mg. %)	Creatinine (mg. %)	Uric Acid (mg. %)	Phosphorus (mg. %)	CO ₂ Content (vol. %)	Chlorides (NaCl) (mg. %)	Icterus Index	Total Proteins (Gm. %)
Control*	142	5.8	10.1	3.0		468	12	5.0
2 hours { A.	141	5.9	9.8	2.0	30.5	515	12	4.8
{ B.	53	3.8	6.6	1.2	27.0	538	15	4.7
4 hours { A.	112	5.1	10.1	2.0	30.0	527	15	4.3
{ B.	40	2.6	4.9	2.1	31.0	573	21	4.3
6 hours { A.	87	5.1	8.6	2.0	26.0	573	15	4.4
{ B.	56	3.1	5.6	1.6	26.3	632	21	3.7
8 hours { A.	92	4.7	7.2	2.0	28.0	620	20	4.6
{ B.	52	2.8	4.9	1.5	25.6	550	20	4.6

Contents of Bath Fluid (mg. %)

	Urea Nitrogen	Creatinine	Uric Acid	Phosphorus
2 hours	17	1.2	...	1.6
4 hours	36	1.6	1.8	1.5
6 hours	56	2.1	2.4	2.0
8 hours.	59	2.5	2.9	2.0

* Control chemistries were drawn six hours prior to treatment with artificial kidney.

A. = Blood sample from radial artery en route to machine.

B. = Blood sample following dialysis from machine to brachial vein.

except for albuminous material in Bowman's space. The severest degenerative changes were found in the loops of Henle and distal convoluted tubules which contained hemoglobin casts. Areas of necrosis and regenerating tubular epithelium were present. The cortex and medulla showed focal infiltration with chronic inflammatory cells. The blood vessels were congested with few antemortem thrombi.

Examination of the brain was not made.

Comment. The artificial kidney was applied after nine days of oliguria and progressive uremia. The urinary output

of these retention products in the bath fluid increased concomitantly. The carbon dioxide content of the serum diminished slightly; serum chlorides gradually rose. There was little change in the total protein of the serum; the protein content of the bath was not determined. A slight degree of hemolysis was indicated by the increase in icterus index of the serum during dialysis. Although the level of serum phosphorus remained unchanged, appreciable quantities appeared in the bath fluid. The plasma glucose level of blood obtained from the

radial artery rose from 80 mg. per cent prior to treatment to 280 mg. per cent at the end of treatment.

The downhill course of the patient continued following dialysis. However, the urinary output continued to increase. The day following treatment with the artificial kidney signs of meningeal irritation appeared. Xanthochromic fluid containing many red cells were obtained by lumbar puncture. The bleeding was ascribed to either heparin and/or uremia. Of interest in this regard is the concept of Globus²³ that cerebral softening antecedes cerebral bleeding. This patient, fifty-six years of age, and B. C., sixty-two years of age, manifested intracranial bleeding. When loss of vascular structure or support has occurred, potentiation of hemorrhage by heparin may be anticipated. Jorpes has stressed the large doses of heparin that may be administered to animals and man without producing hemorrhage as long as vessel walls remain intact. Consequently, heparinization appears less hazardous in younger age groups.

It is our impression that restitution of kidney function might have been accomplished in this patient had we started to use the artificial kidney sooner. In addition smaller doses of heparin appear to be indicated, especially in older patients in whom degenerative vascular changes may have occurred.

CASE VI. L. M. was transferred to the Mount Sinai Hospital in November, 1947, because of anuria and marked oliguria of five days' duration. His past history included an appendectomy in 1943 and myocardial infarction in 1944. Chronic cholecystitis and cholelithiasis were known to be present since 1945. The patient was admitted to another hospital where cholecystectomy was performed and a gallbladder full of stones was removed. The operation was uneventful and the blood pressure was well maintained. On the first postoperative day the patient's condition was satisfactory and he voided 400 cc. of urine. On the second postoperative day he suddenly developed a fever of 106.6°F. followed by a precipitous fall in blood pressure to 76 mm. Hg systolic. The blood

pressure hovered around that level for the next forty-eight hours. No urine was voided during the second and third postoperative days. After forty-eight hours of shock the blood pressure gradually rose to a high of 172 systolic and 95 diastolic. There was no subsequent fall. No urine was voided except for approximately 30 cc. per day on the fourth and fifth postoperative days. The abdomen remained soft; the wound was examined and probed, but no abnormality was noted. Blood cultures were negative. A right lower lobe pneumonia was treated with penicillin. As the anuria persisted the blood urea nitrogen rose to 114 mg. per cent. No urine could be obtained from either renal pelvis by cystoscopy and ureteral catheterization. After five days of anuria the patient was transferred to the Mount Sinai Hospital for treatment with the artificial kidney.

Physical examination revealed an acutely ill, somnolent and somewhat disoriented male. His skin itched. He had constant muscular twitching and Cheyne-Stokes respiration. The temperature was 101°F. The blood pressure was 172 mm. Hg systolic and 95 mm. diastolic. There was no jaundice or peripheral edema. The mouth and tongue were dry. Examination of the lungs revealed coarse rales over the right lower lobe posteriorly, with impaired percussion note over the same area. The lungs were otherwise normal. The heart was normal. The pulse was regular and slow. The abdomen was distended and audible hyperperistalsis was noted. There was a healing upper abdominal incision with retention sutures and drains in the upper angle of the wound. There was no pus on probing of the wound and no wound tenderness. There were no palpable abdominal masses.

Examination of the blood revealed a hemoglobin of 13.8 Gm., white blood count 14,300 with 81 per cent segmented polymorphonuclears, 12 per cent stab cells and 4 per cent lymphocytes. The patient was catheterized on admission and 6 cc. of very bloody urine were obtained. Urinalysis showed a specific gravity of 1.020, protein 3 plus, many casts, leukocytes and red cells. The blood urea nitrogen was 110 mg. per cent on the night of admission and 124 mg. per cent on the following morning. The carbon dioxide content of the blood was 49.1 volumes per cent. The electrocardiogram showed no evidence of recent myocardial infarction. It was believed that the patient had a hepatorenal syndrome following cholecystectomy.

The restlessness, twitchings, convulsive movements and cerebral depression continued to progress. On the morning after admission treatment with the artificial kidney was begun. Heparin (400 mg.) was given intravenously in divided doses prior to the onset of dialysis. Repeated tests of the clotting time failed to show any evidence of clotting within four hours. After one hour of dialysis bleeding developed at the operative site. The oozing persisted and after the second hour of dialysis the blood pressure gradually fell to a level of 90 systolic and 60 diastolic. With the drop in systolic blood pressure, the circulation through the apparatus could not be maintained and dialysis had to be terminated. Three units (1,500 cc.) of whole blood and 6 cc. of 1 per cent protamine sulfate had been given via the collateral inlet of the artificial kidney; two additional units of whole blood were subsequently administered in the next hour. The clotting time reverted to 7 minutes, the oozing stopped and the blood pressure rose to 110 systolic and 70 diastolic within an hour after dialysis was terminated.

Immediately before the start of dialysis the following data were obtained: blood urea nitrogen 107, uric acid 16.7 and creatinine 10.5 mg. per cent. At the end of two hours of dialysis the blood urea nitrogen had fallen to 69, the uric acid to 7.1 and the creatinine to 7.2 mg. per cent. The 100 L. of bath fluid were found to contain 20 mg. per cent of urea nitrogen, 4.8 mg. per cent of uric acid and 2.9 mg. per cent of creatinine. Following dialysis, as the interstitial fluids and the circulating blood once again equilibrated, the blood content of these substances rose again. The blood urea nitrogen determined daily increased steadily to 103, 112, 132 and finally 154 mg. per cent. The carbon dioxide content of the blood gradually dropped to 39.4 volumes per cent.

The morning after dialysis 90 cc. of grossly bloody urine were obtained by catheter. During the next few days the urinary output gradually increased so that twenty-four hours prior to death the patient voided 250 cc. The specific gravity ranged from 1.014 to 1.020. The urine contained albumin, many red, white and epithelial cells and moderate numbers of granular casts. The manifestations of uremia were progressive. The temperature rose to 105°F. and the patient expired on the sixth hospital day.

Postmortem examination revealed acute pulmonary edema. The right coronary artery was found to be the site of an old thrombotic oc-

clusion with resultant infarction of the posterolateral wall of the left ventricle. The right hepatic artery had been ligated surgically and two peripheral infarcts of the liver were present. The kidneys together weighed 560 Gm. and revealed bilateral, subacute cortical necrosis with secondary inflammation and pyelitis. On microscopic examination the entire renal cortex showed severe degeneration and necrosis of the epithelium of the convoluted tubules. The intervening stroma was edematous and infiltrated by lymphocytes and large mononuclear cells. The renal alterations were ascribed predominantly to shock; the influence of ligation of the hepatic artery could not be evaluated.

Comment. This patient had been in chronic shock possibly initiated or aggravated by ligation of a main hepatic artery and consequent focal infarction of the liver. He was in far advanced uremia at the time that therapy with the artificial kidney was instituted. Shortly after large doses of heparin were administered oozing at the operative site was noted. The wound had been repeatedly probed and manipulated by surgeons who were attempting to find a local cause for the fever. It is questionable whether the wound would have bled seven days after operation had these manipulations not occurred. The bleeding led to a fall in blood pressure despite administration of whole blood by the collateral inlet of the artificial kidney. As the blood pressure fell circulation through the kidney became ineffective and stasis occurred in the loops. A controlled volume of blood was returned to the patient and treatment was terminated.

The possibility of shock due to exsanguination of the patient into the machine is counterbalanced by filling the cellulose acetate coils with either blood or saline prior to the start of dialysis. Consequently as blood enters the apparatus displaced blood or saline is returned to the patient. Even a slight excess of inflow over egress causes distention of the tightly wound coils and permits immediate reduction in the volume of blood leaving the patient while return to the patient continues unabated.

The dialysis in this instance was limited to two hours. However, marked diminution

in blood urea nitrogen, creatinine and uric acid were demonstrated even in this short time, illustrating again the dialyzing efficiency of the apparatus.

COMMENTS

We have treated six patients with the artificial kidney; case II was treated twice. Cases I and II are our recent patients; both recovered. Cases III, IV, V and VI constitute the initial group treated with the artificial kidney. They were *in extremis* prior to treatment. However, they served to establish the potentialities of the apparatus and to indicate the advisability of applying the artificial kidney before irreversible changes have occurred.

There can be no doubt that the Kolff artificial kidney is mechanically capable of efficient and rapid dialysis. The exposure of a large surface of blood to a bath fluid of predetermined composition is accomplished by means of the semipermeable membrane of cellulose acetate. Small molecules (up to a molecular weight of approximately 35,000) traverse this membrane. The rate of molecular exchange across the membranes is largely influenced by the relative concentrations of the solutes in blood and bath as well as the duration of exposure of the blood film to the bath fluid. The dialysis is controlled by variation in the composition of the bath. Urea, creatinine, uric acid, sodium, calcium, phosphorus, phenols and substances of similar molecular weight are readily removed; the larger molecules, including the serum proteins, traverse the membrane with difficulty. Any substance in blood capable of freely passing through the membrane may be removed from the blood by omitting it from the bath fluid.

Other types of "artificial kidneys" have been built. The essential principles are similar in all. The variations depend upon the mechanical ingenuity of the creator. However, all types require the use of heparin to maintain the fluidity of the blood as it passes through loops of cellophane; heparin has made the artificial kidney possible. However, its shortcomings

must be kept in mind. Recent surgical operation or other trauma creates the hazard of bleeding due to heparinization. Large doses of heparin had been advocated to prevent coagulation in the apparatus.¹² We soon learned that this dosage is excessive. Our first patient (Case II), a sixty-three year old male, was given 820 mg. of heparin in four hours. Postmortem examination revealed small hemorrhagic foci in the brain. A fifty-six year old male (Case III) was given 700 mg. of heparin intravenously over an eight-hour period. Permission to examine the brain at autopsy was denied. However, xanthochromic fluid was obtained by lumbar puncture. The predisposition of these older patients with uremia to hemorrhage is well known and caution in heparinization is essential. A young woman (Case III) was given 450 mg. intravenously in one hour. At autopsy she showed no evidence of intracranial bleeding. No significant visceral hemorrhage was found in any case. We now use 100 to 200 mg. of heparin intravenously at the start of dialysis, followed by 50 to 100 mg. intravenously as determined by hourly determinations of the clotting time. A coagulation time of at least one to two hours during the treatment appears desirable. Whole blood, toluidine blue and protamin are available at all times as heparin-antagonists.

The literature contains descriptions of various methods of dialysis. These include perfusion of intestinal loops, serous surfaces and synthetic membranes. It is not the purpose of this paper to evaluate the relative merits of these methods. The end sought by each means is identical. However, use of an apparatus which permits dialysis outside of the body is more benign than other measures which either require major surgical intervention or have the obvious hazard of causing infection. Even the use of a Miller-Abbott tube and continued irrigation of the intact intestine¹¹ is a tedious and troublesome process usually complicated by diarrhea which further disturbs water and electrolyte balance.

It is our intention to employ the artificial

kidney in those patients with acute non-obstructive anuria who fail to respond to conservative, well directed medical management. Murray¹⁸ has noted the poor results obtained in animals which are allowed to become moribund prior to the onset of therapy. Our experiences also indicate that irreversible changes must not be permitted to occur before dialysis is undertaken. We have stressed elsewhere the relatively high incidence of spontaneous diuresis in acute non-obstructive nephropathies and have urged care in maintaining electrolyte balance and avoidance of circulatory embarrassment by overzealous administration of fluid. When it becomes apparent that medical measures are failing, artificial dialysis should be considered. It is obvious that this treatment is not curative but can aid in prolonging the patient's life until spontaneous regeneration of the damaged renal tissue may occur. By the same token it is obvious that the artificial kidney should be reserved for those cases in which restoration of renal function can be anticipated rather than for cases of chronic progressive renal disease.

SUMMARY

The Kolff artificial kidney was used in six cases of acute uremia caused by non-obstructive nephropathies. Clinical histories and laboratory data are presented in detail. The apparatus was shown to be mechanically competent. Its sphere of usefulness is described.

Acknowledgments. During the course of these investigations the authors received assistance and guidance from friends and colleagues too numerous to mention individually. Special thanks are due to Drs. G. Bachr, I. Snapper, W. J. Kolff and S. Jarcho. Drs. M. Steinberg and J. Priver rendered administrative assistance. Dr. H. Sobotka and Miss M. Reiner supervised the many chemical analyses performed by their staff.

REFERENCES

1. KOLFF, W. J. The artificial kidney. *J. Mt. Sinai Hosp.*, 14: 2, 1947.
2. FISHMAN, A. P., KROOP, I. G., LEITER, H. E. and HYMAN, A. The management of acute mercury intoxication. *New York State J. Med.*, in press.
3. LEITER, H., KROOP, I. G., FISHMAN, A. P. and HYMAN, A. The management of acute non-obstructive uropathies. *J. Urol.*, in press.
4. KROOP, I. G., LEITER, H. E., FISHMAN, A. P. and HYMAN, A. The management of acute renal insufficiency following transfusion reaction. *J. Mt. Sinai Hosp.*, to be published.
5. ABEL, J., ROWNTREE, W. C. and TURNER, B. B. On the removal of diffusible substances from the circulating blood of living animals by dialysis. *J. Pharmacol. & Exper. Therap.*, 5: 275, 1914.
6. HAAS, G. Die Methodik der Blutausschwaschung (Dialysis in vivo). *Abderhalden's Handbuch der biologischen Arbeitsmethoden*, 5: 717, 1935.
7. NECHULES, H. Ueber Dialysieren des strömenden Blutes am Lebenden. *Klin. Wchnschr.*, 2: 1257, 1888, 1923.
8. ROSENAK, S. and SIWON, P. Experimentelle Untersuchungen über die peritoneale Ausscheidung harnpflüchtiger Substanzen aus dem Blute. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 39: 391, 1926.
9. FRANK H. A., SELIGMAN, A. M. and FINE, J. Treatment of uremia after acute renal failure by peritoneal irrigation. *J. A. M. A.*, 130: 703, 1946.
10. GOODYEAR, W. E. and BEARD, D. E. The successful treatment of acute renal failure by peritoneal irrigation. *J. A. M. A.* 133: 1209, 1947.
11. OPPENHEIMER, G. D. and ROSENAK, S. Intestinal irrigation in the treatment of certain types of uremia. *J. Mt. Sinai Hosp.* 14: 5, 1948.
12. KOLFF, W. J. New Ways of Treating Uremia. Artificial Kidney and Intestinal Lavage. London, 1947. J. & A. Churchill, Ltd.
13. ROGERS, J. W., SELLERS, E. A. and GORNALL, A. G. Intestinal perfusion in the treatment of uremia. *Science*, 106: 108, 1947.
14. PENDLETON, W. R. and WEST, F. E. The passage of urica between the blood and the lumen of the small intestine. *Am. J. Physiol.* 101: 391, 1932.
15. THALHIMER, W. Experimental exchange transfusion for reducing azotemia. Use of artificial kidney for this purpose. *Proc. Soc. Exper. Biol. & Med.*, 37: 641, 1938.
16. ALWALL, N. On the artificial kidney. I. Apparatus for dialysis of the blood in vivo. *Acta med. Scandinav.*, 128: 317, 1947.
17. ALWALL, N. and LEMBIT, N. On the artificial kidney. II. The effectivity of the apparatus. *Acta med. Scandinav.*, 196: 250, 1947.
18. MURRAY, G., DELORME, E. and THOMAS, N. Development of an artificial kidney. *Arch. Surg.*, 55: 505, 1947.
19. REINER, M. Manual of Clinical Chemistry. New York, 1941. Interscience Publishers.
20. GONZALES, T. A., VANCE, M., HALPERN, M. and MARTLAND, H. Legal Medicine and Toxicology. New York, 1937. D. Appleton-Century Co.
21. LONGCOPE, W. T. and LUETSCHER, J. A., JR. Clinical uses of 2,3 dimercaptopropanol (BAL). XI. The treatment of acute mercury poisoning by BAL. *J. Clin. Investigation*, 24: 557, 1946.
22. LUCKÉ, B. Lower nephron nephrosis. *Mil. Surgeon*, 99: 371, 1946.
23. GLOBUS, J. H. and STRAUSS, I. Massive cerebral hemorrhage; its relation to pre-existing cerebral softening. *Arch. Neurol. & Psychiat.*, 18: 215, 1927.
24. JORPES, J. E. Heparin in the Treatment of Thrombosis. New York, 1946. Oxford University Press.

Transperitoneal Lavage for Twenty-six Days in the Treatment of Azotemia*

G. K. FENN, M.D., L. A. NALEFSKI, M.D. and J. LASNER, M.D.

Chicago, Illinois

EVER since the introduction in 1914 by Abel, Rowntree and Turner¹ of the artificial means of removing substances ordinarily excreted by the kidney, considerable attention has been focused on newer and more satisfactory means of combating azotemia. It is a well known fact that when the blood concentration of non-protein nitrogen and urea is elevated these substances will be excreted into the intestinal tract. Advantage of this fact was taken by the use of gastroduodenal lavage and the production of diarrhea with only moderate success. Suggestions for the use of isolated loops of intestine subjected to continuous lavage seem for the moment doomed to failure since studies to date indicate that over 10 feet of bowel as an isolated segment would be required to supply 10 per cent of maximum normal renal clearance (75 ml. per minute). The procedure is at present still being studied by Kolff who hopes to succeed in this with the use of proper dialyzing fluids and diet. Ochsner has suggested that the employment of gastroduodenal lavage may be a solution to the problem. However, completed studies employing this method have not been reported. Kolff and Berk² have recently popularized the "vivi-diffusion" method in treatment of azotemia. This procedure involves the use of some 25 to 30 meters of cellophane-like material similar to sausage casing (which is a permeable membrane) submerged into a container filled with a salt solution that can be varied with the changing blood chemistry of the patient. In this manner the

blood proteins are preserved and acidosis and other acid-base factors can be more readily controlled. Blood is introduced into the unit from a cannulated artery and is allowed to trickle over the extensive surface area (20,000 sq. cm.) presented by the cellophane tubing. As the blood flows through the tubing, dialysis takes place and an equilibrium is established between the blood and the extratubular fluid. In this manner the nitrogenous products which are crystalloids are removed from the blood stream. The blood is then readmitted into the circulation by pumping it into a vein. Naturally, this procedure calls for having the patient well heparinized. This unit is very efficient but the technicalities involving the use of this procedure, construction and operation of the unit are responsible for its rather limited use and acceptance. Still other methods for treating azotemia are decapsulation,^{3,4} high splanchnic block⁵ and the use of large doses of heparin. The latter procedure is advocated by Kallner⁶ and shows promise in selected cases. Decapsulation is of unquestionable value when edema of the kidneys precludes their function because of compression of the renal parenchyma. Peritoneal lavage was introduced by Ganter in 1923⁷ and has been resorted to clinically on numerous occasions. At least twenty-two cases have been reported in the literature and eight recoveries can be attributed to its use.

The need for some temporary renal substitute occurs only when reversible or non-permanent damage or insult involves the

* From Medical III and Surgery IV Service, St. Luke's Hospital, and Northwestern University School of Medicine, Chicago, Ill.

kidneys. These occasions are those involving hemolytic crisis following the infusion of improperly typed blood, toxic sulfa reactions, mercurial poisoning, crush syndromes, burns and other forms of urinary tract disease in which the ultimate prognosis is fair if the immediate crisis can be met. Truetta⁸ has pointed out that renal anoxia, found in a number of pathologic conditions, was probably the result of overstimulation of the vascular nerves. He further showed that by peripheral reflex and direct stimulation the renal cortex of the kidney became completely ischemic. He concluded by noting that under such conditions the flow of urine is decreased or may be entirely suppressed. His implications are that "nervic stimulation could be produced centrally or peripherally by a variety of noxious agents and the picture seen in many loosely related syndromes—e.g., 'sulfa-kidney,' incompatible-transfusion kidney, Weil's disease, and some forms of nephritis—is the result of a defense device by which the cortex of the kidney is excluded from the circulating toxin or other noxious agents and thus protected." Too prolonged operation of the device results in permanent damage. This concept of a functional change-over under various conditions to a medullary renal circulation has obvious physiologic, pathologic and clinical implications. For instance, the interpretation of renal function tests must be considered. The pathology of hysterical uremia, emotional anuria, post-abortion and post-traumatic uremia, and the response of these last two to splanchnic block are readily explained. Olson and Necheles called attention to the controversy over the mechanism of impaired renal function.⁹ It was pointed out that a number of patients with peptic ulcer, who had normal renal function before treatment with calcium carbonate, developed marked depressed renal function during alkalosis. The Army Malaria Research Unit at Oxford¹⁰ described the effects of large doses of alkali in normal men and found that all subjects had disturbances of renal function. Baker and Dodds¹¹ theory of acidosis pre-

cipitating acid hematin with subsequent mechanical block in the tubules has been subjected to considerable criticism. This, of course, is the basis for the alkalosis therapy. Wakeman¹² states that there is no support for the theory that acidosis in blackwater fever is an indication for alkaline therapy. Foy and Kondi¹³ described cases of anuria frequently developing in patients who had slight hemolysis and passed alkaline urines and other patients who failed to develop anuria although they had marked hemolysis with an acid urine. In 1943 these workers¹⁴ carefully reviewed the alkalization hypothesis and concluded that there was insufficient evidence to warrant any statement as to the efficiency of alkaline solutions in either preventing or relieving the oliguria and anuria in blackwater fever, incompatible transfusions and crush injuries. However, the institution of the alkaline therapy very early in hemolytic accidents before oliguria or anuria become apparent may be the reason for its so-called success in many cases. The same may hold true for the intravenous use of isotonic sodium sulfate as described by Olson and Necheles.⁹ At any rate, it is evident that considerable confusion exists in the understanding and treatment of oliguria and anuria whether it be from the more common sequelae or from other more remote complications.

Transperitoneal lavage has been studied very carefully by a number of investigators.^{15,16,17} Fine, Frank and Seligman^{18,19,20} have been pioneers in this procedure and have reported their results elsewhere. Ganter's original work in 1923 has been improved upon by these authors with the institution of continuous lavage and the use of lavage fluid more closely resembling the electrolyte composition of extracellular fluid. The lavage fluid must be considered carefully insofar as the blood chemistry of the patient can and will be altered by changing its composition. By making the fluid hypo- or hypertonic, the blood stream and hence the extracellular fluid will react in the usual manner. Generalized edema and especially pulmonary edema can thus

be regulated and controlled by it. The composition of the lavage fluid as suggested by Seligman et al.²⁰ is a modified Tyrode's solution. It is reputed to be especially effective in combating acidosis, but that this does not hold will be illustrated by the

thus accomplish dehydration. Dehydration can be still further increased by eliminating all sodium salts from the lavage fluid.

The apparatus used in the case reported here follows that of Fine et al. very closely. Several minor variations were introduced

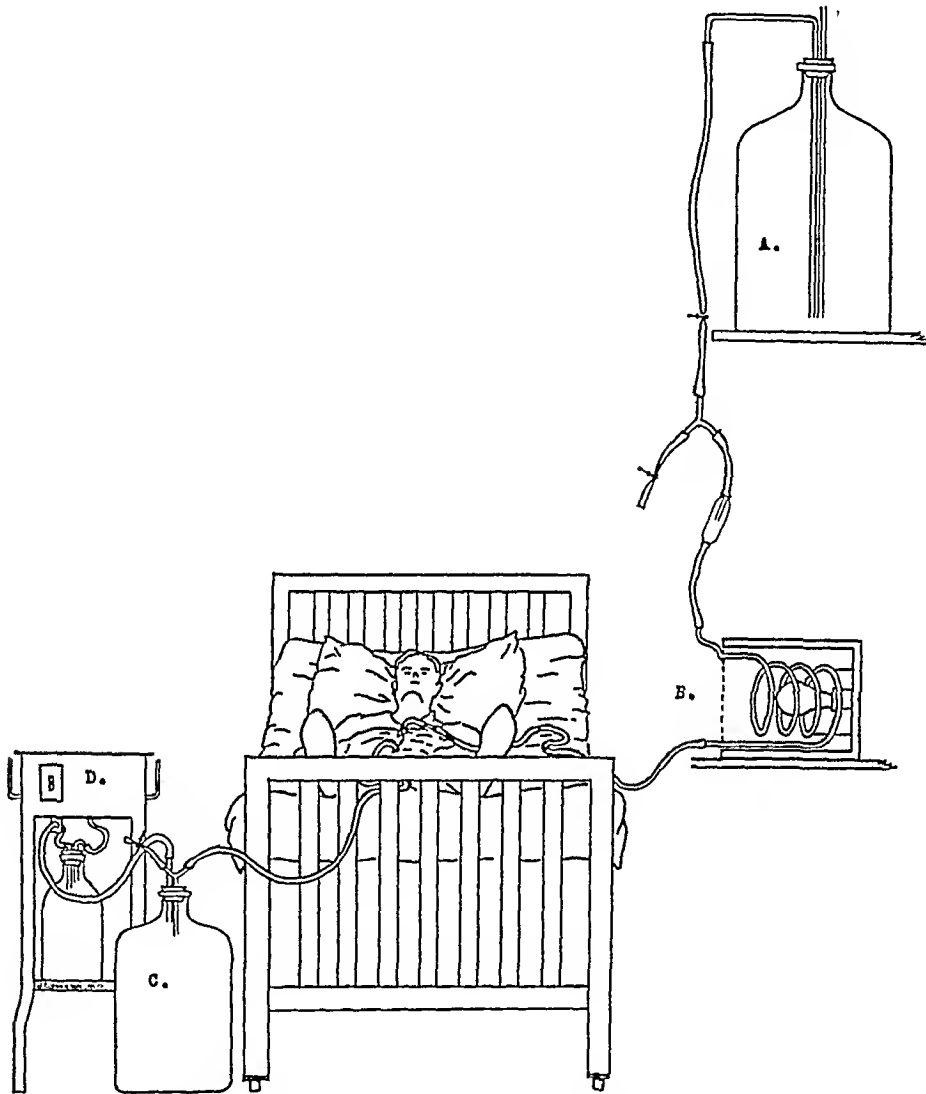


FIG. 1. This illustrates the simplicity of the apparatus used in transperitoneal lavage. A is the constant head siphon storing the influent lavage fluid; B shows the details of the heating unit used to bring the lavage fluid to body temperature; C is the effluent lavage fluid container; D is the suction pump.

case we are reporting. Slight alterations of the composition of this fluid, as by the addition of greater amounts of glucose, will provide nearly all of the caloric requirements of the patient and hence eliminate the necessity of parenteral administration of fluids of this sort and thus limit the possibility of pulmonary edema. Should pulmonary or generalized edema develop the fluid can be made hypertonic with 5 per cent gelatin and 2.5 per cent glucose and

which we believe were of value. One of these was the method used in bringing the lavage fluid to body temperature. This consisted of a small wooden box, measuring about 1 cu. ft., in which was mounted a lamp socket and lamp. About 4 feet of $\frac{3}{8}$ in. copper tubing was coiled closely around the lamp. It was found that a lamp of about sixty watts was sufficient to raise the temperature of the lavage fluid from room to body temperature. This procedure con-

served approximately 500 calories of body heat per day as well as provided a more homeostatic character to the lavage fluid. Once the lavage fluid was started the temperature adjustment required no further attention. The heating unit could be conveniently placed in bed with the patient. Another variation was the introduction of a constant head siphon in the lavage fluid storage bottle. This provided a constant flow to the fluid and once set need not be changed or adjusted. A number of different types of suction pumps was used to remove the lavage fluid from the peritoneal cavity, but the one thought to be most satisfactory was the Thermotie Drainage Pump.* This pump provided ample suction without danger of trauma to the viscera and also had the added feature of being entirely noiseless. The lavage fluid was prepared in ordinary 5 gallon carboy bottles and mounted on a platform stepladder about 3 feet above the patient. The bottles were sterilized before each batch of lavage fluid was prepared by inserting them into the dressing room steam sterilizer on the ward floor. They were filled with freshly distilled water without any further efforts to sterilize the water. Tyrode's solution was prepared in accordance with the suggestions of Fine *et al.* and added to the distilled water. Figure 1 illustrates the equipment used by us.

CASE REPORT

On March 7, 1947, C. H., a thirty-one year old colored male, was admitted to St. Luke's Hospital, Chicago, in a confused state following two convulsive seizures. His wife who accompanied the patient left before any history could be elicited. The patient was irrational to the extent that he did not know nor realize where he was, hence no history pertaining to his illness could be obtained from him. His blood pressure upon admission was 240 systolic and 140 diastolic, pulse 90 and temperature 99.2°F. rectally. Respirations were 25 per minute and labored. His chest had a few moist rales in both bases. The liver was 3 cm. below the costal

margin. There were no neurologic findings. Venesection was performed and aminophyllin and sedation given. The usual emergency laboratory tests were negative and the impression was that of a hypertensive encephalopathy.

The following day additional history was obtained from his wife. She stated that the patient had been quite well except for a cold from which he had recovered. She added that he was a known hypertensive but had been without symptoms until three days preceding his admission. On the day of admission he awoke complaining of epigastric pain and nausea. He did not vomit. This continued and was unrelieved by a cathartic; the patient was taken to his own doctor who told him that he needed digitalis. That morning he took two tablets and a second similar dose at noon. About this time he complained of blurring of vision and some mental confusion. About 2 P.M. he had a convulsive seizure which his wife described as beginning with a cry and followed with a spastic type of condition immediately preceding a more dynamic type of convulsion. The description was that of a rather typical grand mal seizure. It had a duration of about two minutes or less. There was a second seizure an hour or so later and the patient was then brought to the hospital arriving about 5:00 P.M. The patient never had convulsive seizures in the past.

He was known to be hypertensive for the past four years. At this time he was employed at the Duke University Hospital. It was here that his hypertension was discovered. An operation was considered and then decided against. The patient had been on a low salt, low protein diet since that time. He had one or two episodes of ankle edema and became dyspneic with slight exertion. He did not complain of orthopnea, chest pain, cough or hemoptysis. To anyone's knowledge he did not have nephritis, but it was stated by his wife that all of his family died of so-called "heart dropsy." The patient was born and reared in North Carolina and left there eighteen months before his admittance to our hospital.

Inventory by systems revealed that the patient neither gained nor lost weight. His health was considered "precarious." He had had severe headaches on exertion ever since childhood. He had one very sore throat when a child which kept him in bed for two weeks. The gastrointestinal review was negative except for the pain and nausea described in the history and

* Manufactured by the Gomco Surgical Manufacturing Company.

constipation for which he used numerous laxatives. The genitourinary system was normal with the exception that the patient was bothered with frequency and nocturia. For this reason he avoided fluids after eating his evening meal.

His past history revealed that he had the usual childhood diseases. There was no history of nephritis or rheumatic fever, neither was there any history of surgery.

His personal history revealed that he was a butler, that he used tobacco only occasionally, did not use alcohol and that he remained constantly on a salt poor and low protein diet. His appetite was described as being poor.

Physical examination at this time revealed a well developed, well nourished colored male about thirty-one years of age lying quietly in bed somewhat confused and very somnolent. The external ocular movements were normal; pupils were round and equal but reacted sluggishly to light and accommodation. Fundusoscopic examination revealed a hypertensive retinitis grade 3. There were no new hemorrhages. The ears, nose, throat and neck were essentially normal. His lungs were now clear to percussion and auscultation and tactile fremitus was bilaterally equal. The heart sounds were markedly accentuated. The rhythm was regular and the rate was 100. The apex was found to be 2 cm. to the left of the mid-clavicular line. No murmurs were heard in any of the stations with the exception of some roughening of the first tone at the apex. There was no friction rub. The blood pressure at this time was 238 systolic and 112 diastolic. The liver, kidneys and spleen were not palpated. There was no abdominal tenderness or rigidity and no evidence of any mass in the abdominal cavity. The bowel sounds were normal. The bladder was not distended and there was no costovertebral tenderness. The genitalia were normal and there was no evidence of edema. Neurologically, the reflexes were bilaterally equal and physiologic. The cranial nerves were all intact and no pathologic reflexes were found.

The morning after admittance the patient remained in a semi-stuporous condition. He voided 400 cc. at noon and later the same day was catheterized to check for obstruction and 40 cc. of urine were obtained. The urethra was patent throughout. At 5:00 P.M. the same day he again voided 200 cc. Laboratory reports at this time showed a red blood count of 2,080,000; white blood count 14,900; hemoglobin 6.8 Gm.

per cent; non-protein nitrogen 150 mg. per cent; creatinine 11.9 mg. per cent; CO₂ combining power 54 volumes per cent; icteric index 2.0. His total urinary output for that day was 640 cc.

The following day he voided 100 cc. and none the following two days. An electrocardiogram indicated myocardial damage on a hypertensive basis. His blood chemistry now showed a rapid increase in nitrogenous products with his anuria and on the fifth hospital day had this picture: non-protein nitrogen 258 mg. per cent; urea 203 mg. per cent; creatinine 22.2 mg. per cent; total protein 5.6 Gm. per cent; calcium 9.6 mg. per cent; phosphorus 13.8 mg. per cent. In addition his red blood count had fallen to 1,080,000; white blood count was now 19,000 and hemoglobin 4.3 Gm. per cent. A differential white count showed 94 per cent polymorphonuclear leukocytes and 6 per cent lymphocytes. The urine voided on the second hospital day was acid in reaction and had a specific gravity of 1.008, 100 mg. per cent plus albumin, 2 plus red blood cells and 3 plus white blood cells. It was negative for sugar and showed occasional granular and hyaline casts.

Prior to this time the patient had already showed uremic frost and all of the other clinical signs of a full blown uremia. A portable KUB plate made on the second hospital day indicated a possibility of a renal stone in the left renal pelvis. It was very evident that the patient's condition was at the terminal stage. No specific diagnosis had been made up to this time. Several of the more obvious diagnoses were considered, among them polycystic kidneys and a malignant nephrosclerosis. Still it was believed that this could be a reflex anuria on the basis of a stone somewhere in the genitourinary tract. A renal stone in the presence of already damaged kidneys could explain the clinical picture presented by this patient. With the strong impression that the possibility of recovery was remote, the patient was subjected to continuous transperitoneal lavage in order to reduce his azotemia.

With the patient in bed and under local anesthesia two midline incisions were made. One, for the influent lavage tube, was placed mid-way between the xiphoid process and the umbilicus. The effluent side was placed approximately 4 cm. above the symphysis pubis. A better positioning of these tubes would have been to place them in either flank as shown by other investigators. The influent tube consisted of ordinary laboratory rubber tubing

$\frac{3}{8}$ in. in diameter with multiple perforations. The tubing was about 6 inches long. The effluent tube was a stainless steel sump drain with multiple perforations. It was directed toward the cul-de-sac. The lavage fluid consisted of the following amounts of anhydrous materials per

of fibrin which formed in spite of the initial dosage. This amount of heparin did not alter the patient's bleeding time.

Seligman *et al.*²⁰ in his work with dogs found that the most efficient rate of lavage was somewhere between 25 and 40 cc. per minute, re-

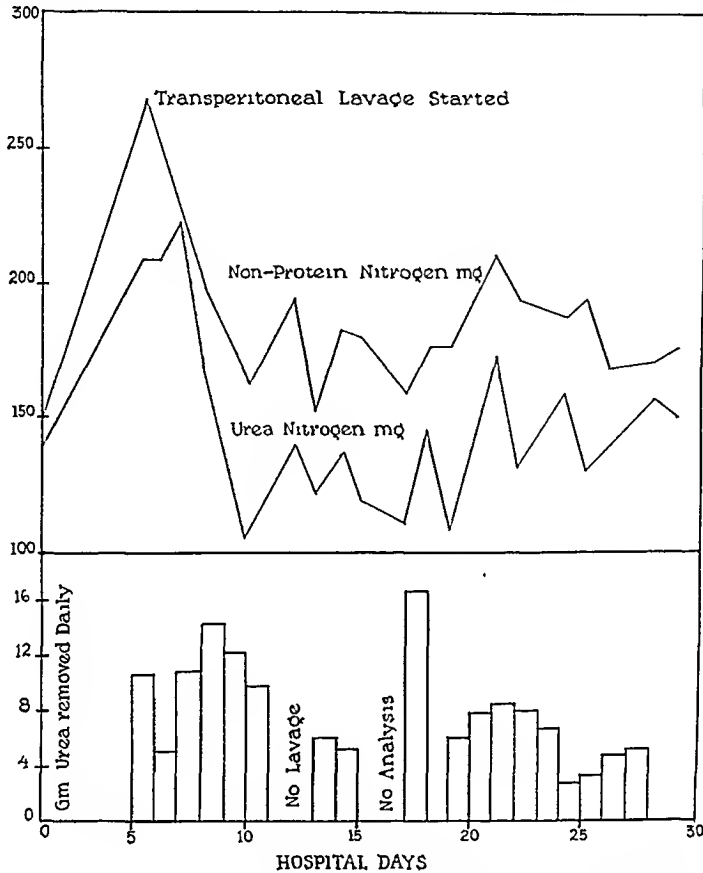


FIG. 2. The above curves illustrate the trend of the concentration of non-protein nitrogen products in the blood as well as the daily amounts of urea removed by lavage.

liter of fluid: sodium chloride, 8.0 Gm., potassium chloride 0.2 Gm., calcium chloride 0.1 Gm., magnesium chloride 0.1 Gm., sodium dihydrogen phosphate 0.05 Gm., sodium bicarbonate 1.0 Gm. and dextrose 1.5 Gm. In addition 10,000 units of sodium penicillin and 0.14 Gm. of sodium sulfadiazine were added per liter of lavage fluid to combat any contaminants which might be introduced into the fluid during their preparation. It is believed that these were most important in averting or at least delaying the onset of peritonitis. Sodium heparin in a concentration of 0.5 mg. per cent was added to minimize the formation of fibrin and thus prevent the tubes from becoming clogged. It was later found necessary to double this dose of heparin to prevent the small amount

quiring a total of 36 to 58 L. of fluid per day. Volumes below this were inefficient and volumes above were of no particular benefit. We planned to pass 40 L. per day through this patient. Putting this amount of fluid through the peritoneal cavity presented no problem as long as the suction pump continued to remove it. Much larger volumes could have been passed had it been necessary.

When the lavage was started the non-protein nitrogen reached a high of 266 mg. per cent, the urea 248 mg. per cent and creatinine 23 plus mg. per cent. Figures 2 and 3 illustrate the results obtained with the lavage. It will be seen that a rather rapid drop from the high nitrogenous values was quickly realized. The later more gradual drop was due in part to pump

failure and also short-circuiting of the lavage fluid. Upon investigation the influent tube was found lying anterior to the omentum. It is believed that if placed posterior to it more dialyzing surface would be available and thus more nitrogenous products would be removed.

the usual vitamins in large doses. The anemia was controlled as long as transfusions were available.

The patient showed marked improvement clinically the second day after lavage was instituted. He became rational, his appetite im-

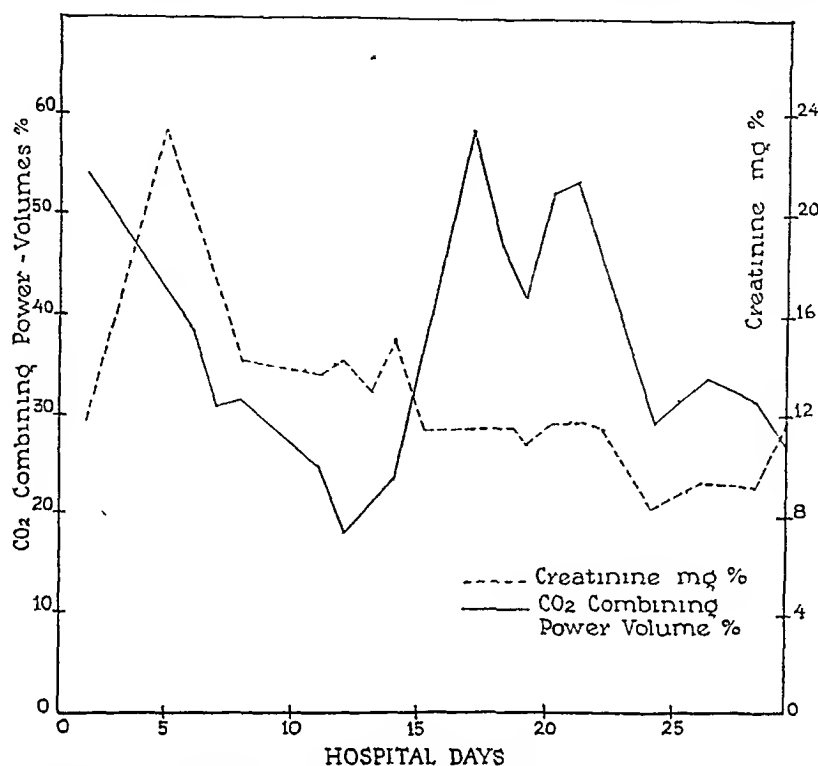


FIG. 3. Illustrating the blood creatinine levels and CO₂ combining power.

It was found that a considerable amount of difficulty was experienced in keeping the effluent tube in the cul-de-sac. Since it kept working itself to the surface, it was finally allowed to remain in that position at which time a definite track was formed about it by the omentum. It worked very well in this position. Had the tube been directed to the cul-de-sac from the flank position instead of from the midline, this earlier difficulty might have been avoided. On the fourteenth day of lavage the flow was interrupted for thirty-six hours. The non-protein nitrogen and urea nitrogen blood levels again showed a rapid rise. This was reduced when lavage was resumed. Acidosis was a problem early in the treatment contrary to expectations with the use of buffered lavage fluid. However, this was easily corrected with the use of sixth molar sodium lactate solution. The patient was only mildly edematous from time to time in spite of the rather large volumes of intravenous fluids used to correct the marked anemia, acidosis and to stimulate diuresis. During the entire period, penicillin was given intramuscularly as well as

proved and he tolerated food very well. He did not object to the treatment and from time to time would aid in the adjustment of the apparatus. On the eighth day of peritoneal lavage he developed an ileus. Wangenstein suction was started and continued for seven days. At the end of this time bowel sounds returned and the patient resumed taking food well and having normal bowel movements. On the eleventh day of lavage his blood pressure dropped from its usual high level and remained at 160 systolic and 110 diastolic. The blood creatinine showed the most constant drop throughout the period of treatment. This would be expected insofar as it is the last to rise in renal failure. The non-protein nitrogen and urea nitrogen did not show the rapid and steady decrease in the latter half of the treatment as it did in the beginning. This probably was due to the fact that there was a rapid unloading of nitrogenous products from the extracellular fluid stored there during the height of azotemia and also because of the high protein diet and parenteral administration of amino acids during

the later stages of treatment given to combat emaciation.

At no time was the urinary output sufficient to sustain life. The patient became anuric on the third hospital day and remained so until the third day of lavage. At this time he voided 420 cc. which was encouraging. The urine proved to be of better quality than we anticipated. The specific gravity was 1.016 and contained 0.5 Gm. of urea. It was free from sugar but did contain 300 mg. per cent of albumin, some red blood cells and granular and hyaline casts. The specific gravity and urea content did indicate some functioning renal tissue. The following sixteen days he averaged a urinary output of 150 cc. per day. After this time his output became progressively less and during the final three days of treatment was only 50 cc. per day. This obviously was insufficient to prevent azotemia.

Calculations for blood urea clearance by lavage of the peritoneum showed that our set-up was not as efficient as that reported by Seligman and his group.²⁰ The maximum clearance we could attain was 11.0 cc. of blood per minute. Our average clearance was in the vicinity of 8.5 cc. of blood per minute.

The effluent lavage fluid had the appearance, color and odor of urine. It always had a slight turbid appearance which was due to fibrin and other proteins. Only a trace of protein could be demonstrated at any time. The specific gravity was unaltered in passing through the peritoneal cavity. It was found to be sterile on all occasions with the exception of the eleventh day of lavage. This was the third day following the onset of the ileus. Culture of this effluent lavage fluid showed a medium growth of *Bacillus alkaligenes* and *Pseudomonas pyocyaneus*. Cultures on later days failed to confirm this. At the time the lavage was temporarily interrupted on the fourteenth day of treatment, 1.0 Gm. of streptomycin in 1 L. of lavage fluid was instilled into the peritoneal cavity without untoward effects. The blood sulfadiazine level never exceeded 2.4 mg. per cent. In the earlier days of treatment when the dextrose content of the lavage fluid was maintained at 1.5 Gm. per L. practically all of it was absorbed. Later, when a more hypertonic solution was used to combat edema and nutritional acidosis, the dextrose content was increased to 20.0 Gm. per L. At this concentration the peritoneum failed to absorb all of the sugar. Approximately 40 to

50 per cent passed through with the effluent fluid unabsorbed.

With the onset of the twenty-second day of lavage the patient became progressively more edematous. Pulmonary edema did not become evident until the twenty-sixth day of lavage. At this time the patient became more dyspneic and in spite of all measures suddenly expired.

The autopsy findings were in accordance with our earlier impressions. The anatomic diagnosis was that of a malignant nephrosclerosis. There was a fibrinous and fibrous peritonitis, pleuritis and pericarditis, marked hypertrophy and cloudy swelling of the myocardium and dilatation of the left ventricle. There was a bilateral hydrothorax. In addition there was metastatic calcification of the kidneys and the lining and myocardium of the heart, mural thrombi of the right auricle and right auricular appendage. There was a moderate atherosclerosis of the aorta and its main branches; verrucous endocarditis of the posterior leaflet of the aortic valve, hyperemia of the lungs; cortical adenoma of the right suprarenal gland, fibrous thickening of the aortic, mitral and tricuspid valves; glandular hyperplasia of the prostate.

The histological diagnosis confirmed these findings.

COMMENT

The autopsy findings make it apparent that the kidney damage in this patient was definitely irreversible. It is interesting to note and of definite value, too, that this patient was able to live an additional twenty-six days without material aid from his own renal tissues. His existence during this time was not too trying or uncomfortable. Had the damage been of a reversible nature, twenty-six days would have been more than ample for the damage to be repaired. One of the difficult decisions to make in dealing with patients developing azotemia is when treatment of this nature should be instituted. The proper time has not been established. It is not possible to say when any given data regarding the uremic state signify the existence of irreversible damage. Therefore, since the procedure can be carried on for many days safely, as illustrated by this case, it probably should be

started soon after the azotemia is definitely established. Meanwhile, it is important not to add to the patient's problems by excessive fluid administration since the amount of water needed is small and as a diuretic in anuria it has proved futile.

The maintenance of proper electrolyte balance of the extracellular fluid will probably be the key to success in most cases treated by this method. A common error, as we experienced, is the ambitious administration of parenteral fluids. In retrospect we now appreciate that the only fluids required were those to correct the acidosis and blood transfusions to improve the severe anemia present. Much more accurate information as to the state of hydration of the patient can be obtained from studies of the volume of extracellular fluid by means of radioactive sodium or by the other means now available. These data would be of invaluable assistance in altering the composition of the lavage fluid. Gamble, in a personal communication to Fine, stated that in uremia the defense of the chemical structure of the extracellular fluid is of much more importance from the point of view of survival than reduction of azotemia.

In the past the chief danger considered in this method of correcting azotemia was that of bacterial peritonitis. Here again it has been demonstrated that with reasonable care in the preparation of the fluids and handling of the equipment this hazard can be readily eliminated. The use of penicillin and sulfadiazine salts aids in keeping the solutions sterile. Fine and his group use a bacterial filter interposed between the abdomen and the lavage storage bottle. This was not included in our equipment. Although it is an added protection, it was found to be unnecessary. In those instances in which the kidney has been sensitized to sulfa drugs in the past it will be necessary to avoid using materials of this kind in the lavage fluid. Streptomycin can be substituted in these cases. One culture of the effluent lavage fluid was found to contain *Bacillus alkaligenes* and *Pseudomonas pyocyaneus*. These organisms were

not found on repeated examinations following their initial discovery and may have been eliminated by the streptomycin which was instilled into the peritoneal cavity shortly after their presence was known. During the twenty-six days of operation of this equipment several members of the hospital staff were called upon at various times to prepare solutions, change bottles, etc. In spite of these opportunities for contamination no bacterial peritonitis developed. This may have all been due to the inhibitory action of the antibacterial agents in the lavage fluid as well as the constant dilution and exchange of fluid passing through the peritoneal cavity. Of the recent cases reported in the literature using this form of therapy, none reported the development of bacterial peritonitis as a cause of failure. Therefore, it can be concluded that with reasonable care and caution this hazard may be minimized.

No claim for originality for this method of combating azotemia is made by the present authors. The excellent work of Seligman, Fine and Frank has led to its present day understanding and application. It is apparent from our working with it, as well as other cases reported, that it is still a procedure lacking in perfection. A number of the difficulties will be removed with the development of a more efficient lavage fluid. In the meantime, however, this therapeutic procedure which utilizes the peritoneal membrane for removing non-protein nitrogenous materials from the blood stream and tissues in what would otherwise be a fatal azotemia should be resorted to with caution.

CONCLUSIONS

1. Continuous transperitoneal lavage was carried out for twenty-six days, resulting in a marked reduction of blood non-protein nitrogenous products. This period of time would have been ample for repair of a reversible kidney damage. The case reported had irreversible damage.

2. That a more efficient and better buffered lavage fluid is necessary for its

successful use is indicated by the development of acidosis and edema. Parenteral fluids in any form should be administered with caution.

REFERENCES

1. ABEL, J. J., ROWNTREE, W. G. and TURNER, B. B. On the removal of diffusible substances from the circulating blood of living animals by dialysis. *J. Pharmacol. & Exper. Therap.*, 5: 275, 1914.
2. KOLFF, W. J. and BERK, H. T. J. The artificial kidney: a dialyser with a great area. *Acta med. Scandinav.*, 117: 121, 1944.
3. LYONS, J. H. and RAINES, S. L. Renal decapsulation for transfusion oliguria. *Ann. Surg.*, 122: 894, 1945.
4. FLO, S. C. and CUMMINGS, H. W. Unilateral decapsulation of kidney for transfusion oliguria. *Surgery*, 14: 216, 1943.
5. PETERS, H. R. Anuria following hemolytic reaction to blood transfusion. Recovery following splanchnic block. *Ann. Int. Med.*, 16: 547, 1942.
6. KALLNER, S. Personal communication.
7. GANTER, G. Ueber die Beseitigung giftiger Stoffe aus dem Blute durch Dialyse. *München. med. Wchnschr.*, 70: 1478, 1923.
8. TRUETTA, J. Renal pathology in the light of recent neurovascular studies. *Lancet*, 2: 237-238, 1946.
9. OLSON, W. H. and NECHELES, H. Studies on anuria. *Surg., Gynec. & Obst.*, 84: 283, 1947.
10. Army Malaria Research Unit Oxford. *Lancet*, London, 2: 701, 1945.
11. BAKER, S. L. and DODDS, E. C. Obstruction of the renal tubules during excretion of hemoglobin. *Brit. J. Exper. Path.*, 6: 247, 1925.
12. WAKEMAN, A. M., MORRALL, C. A., EISNMAN, A. J., SPRUNT, D. L. and PETERS, J. P. Metabolism and treatment of blackwater fever. *Am. J. Trop. Med.*, 12: 407, 1932.
13. FOY, H. and KONDI, A. Case of miscarriage following blackwater fever. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 34: 343, 1941.
14. FOY, H., ALTMANN, A., BARNES, H. D. and KONDI, A. Anuria with special reference to renal failure in blackwater fever. incompatible transfusion, and crush injuries. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 36: 197, 1943.
15. WEAR, J. B. and others. Peritoneal lavage in treatment of uremia, experimental and clinical study. *J. Urol.*, 39: 53, 1938.
16. RHOADS, J. F. Peritoneal lavage in renal insufficiency. *Am. J. M. Sc.*, 196: 642, 1938.
17. ABBOTT, W. E. and SHEA, P. Treatment of temporary renal insufficiency (uremia) by peritoneal lavage. *Am. J. M. Sc.*, 211: 312, 1946.
18. FRANK, H. A., SELIGMAN, A. M. and FINE, J. Treatment of uremia after acute renal failure by peritoneal irrigation. *J. A. M. A.*, 130: 703, 1946.
19. FINE, J., FRANK, H. A. and SELIGMAN, A. M. The treatment of acute renal failure by peritoneal irrigation. *Ann. Surg.*, 124: 857, 1946.
20. SELIGMAN, A. M., FRANK, H. A., and FINE, J. Treatment of experimental uremia by means of peritoneal irrigation, *J. Clin. Investigation*, 25: 211, 1949.

Acute Urinary Suppression*

Observations in Twenty-two Patients

RICHARD J. STOCK, M.D.

New York, New York

IN recent years there has been revival of interest in the treatment of acute urinary suppression by a variety of procedures. One approach has been directed toward the alleviation of nitrogen retention and correction of derangements in electrolyte patterns of the blood. The methods employed and the results obtained have been admirably summarized by Snapper.¹ Other efforts have been aimed at increasing urine formation by blocking neurogenic impulses to the kidney or by renal decapsulation, as set forth by Culpepper and Findley.² In the interest of providing a control series it seems timely to review the natural history of acute urinary suppression treated without these means.

The purpose of the present study is to determine the frequency with which severe urinary suppression is spontaneously reversible, to determine the length of time suppression may exist with spontaneous recovery, to record the maximum duration of suppression of urine compatible with life and to ascertain the cause of death in fatal instances.

Definition. Suppression of urine may be said to exist whenever the urinary output for a given period of time falls below the anticipated minimal requirement for urinary water. The magnitude of the solutes requiring urinary excretion and the concentrating ability of the kidney are the two factors that define minimal urine volume. Approximately 500 cc. of urine per day are required by a normal 70 Kg. man under conditions of fasting and thirsting so that

solute retention does not occur, as demonstrated by Gamble.³ This minimal urine volume of 500 cc. per day in the fasting state can be lowered to approximately 250 cc. by daily administration of 100 Gm. of glucose. Such carbohydrate has a protein-sparing action and prevents ketosis. By these two mechanisms the daily solute load and consequently the minimal urine volume are reduced approximately one-half. Further administration of protein and fat only serves to increase the formation of solutes ultimately designated for urinary excretion. For this reason 250 cc. approximates the absolute minimal amount of urine that can be formed under optimum conditions without solute retention. Any additional decrease in urine formation constitutes urinary suppression.

Under conditions of thirsting, with an intake of 100 Gm. of glucose, fluid in the form of urine and insensible water is lost at the expense of preformed body water. Gamble demonstrated that a water intake up to 750 cc. will spare an equivalent amount of preformed body water without increasing fluid loss.³ Any water intake in excess of 750 cc. is excreted in the urine. Thus, in terms of fluid intake for a 70 Kg. man receiving 100 Gm. of glucose daily, suppression of urine occurs whenever the daily urine output is less than 250 cc. plus any water consumed in excess of 750 cc. As many clinical disorders are associated with changes in protein breakdown, solute load and extrarenal water loss, determination of minimal urine volume becomes more

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York N. Y.

complex and the definition of urinary suppression impossible without more specific information.

Selection of Patients. Each case was chosen from the records of the Columbia-Presbyterian Medical Center. Only adult patients

forty-nine days with a urinary output of less than 200 cc. on any one day, and for thirty-one days there was absolutely no excretion of urine whatever. Postmortem examination disclosed complete ureteropelvic obstruction with hydronephrosis due

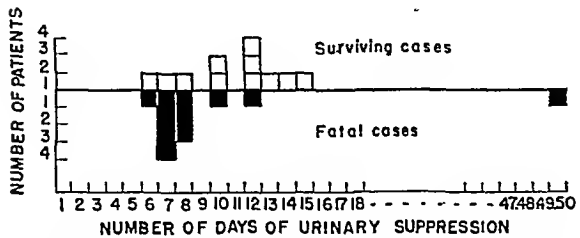


FIG. 1. The duration and outcome of urinary suppression in twenty-two patients.

who had a measured urinary output of less than 100 cc. a day for three or more consecutive days under direct hospital observation were included in this study. In each instance retention of urine within the bladder was excluded by catheterization. Twenty-two patients fulfilling these criteria were found. The various causes of urinary suppression that were encountered in this series are listed in Table I.

Duration. Analysis of the daily urinary output of each individual patient disclosed that diuresis occurred gradually in step-like fashion over a span of four to seven days. It was not until the end of this period that the kidney was able to excrete maximum volumes of urine in the neighborhood of 5,000 to 6,000 cc. It was arbitrarily decided to call the onset of diuresis, or end of a period of urinary suppression, the first day in which the urine volume exceeded 1,000 cc. after a period of three or more days with a urine output of less than 100 cc. daily.

Figure 1 illustrates that in these twenty-two patients the duration of urinary suppression varied between six and fifty days. Eleven patients with severe depression of urine formation lasting from six to fifteen days completely recovered. Eight of these patients exhibited suppression of urine formation for ten or more days. In one patient (G. M., Fig. 2) urinary suppression persisted over a period of more than fifty consecutive days. This patient lived for

TABLE I
FREQUENCY OF VARIOUS CAUSES OF URINARY SUPPRESSION
IN TWENTY-TWO PATIENTS

Cause	No. of Patients
Transfusion with incompatible blood.....	6
Postpartum urinary suppression.....	3
Carbon tetrachloride poisoning.....	2
Diabetic acidosis with shock.....	2
Sulfonamide nephrosis.....	2
Hemolysis due to sulfanilamide.....	1
Mercury bichloride poisoning.....	1
Pentachloronaphthalene poisoning.....	1
Bacitracin toxicity.....	1
Acute glomerulonephritis.....	1
Shock, peritonitis and ileus.....	1
Bilateral ureteropelvic obstruction.....	1

to bilaterally aberrant renal arteries and veins. The capacity of each dilated renal pelvis was not more than 500 cc. With this single exception, urinary suppression did not last longer than twelve days in any of the eleven fatalities. In eight instances death occurred before the eighth day of urinary suppression.

Causes of Death. There were eleven deaths in twenty-two patients, a mortality rate of 50 per cent. An attempt to define the accurate cause of death was made in each fatality. Autopsies were performed on nine patients. In the two instances in which post-mortem examination was refused clinical examination easily ascertained the cause of death—pulmonary edema and generalized peritonitis, respectively.

Table II illustrates that pulmonary infarction, generalized peritonitis and pulmonary edema secondary to excessive fluid administration account for five deaths (45 per cent). Of the remaining six patients two fatalities apparently resulted from multiple causes in which uremia probably played a part. One (A. G., Fig. 3) was a sixty-two year old male whose urinary suppression resulted from severe hemolytic anemia secondary to sulfanilamide sensi-

tivity. This patient died with a serum non-protein nitrogen level of 380 mg. per cent after eight days of urinary suppression. His hospital course was complicated by the appearance of auricular fibrillation with marked congestive cardiac failure and

hospital in coma resulting from a type xxii pneumococcus bronchopneumonia and arteriosclerotic heart disease, with pulmonary congestion, peripheral edema, auricular fibrillation, left bundle branch block and a venous pressure elevation of 230 mm. of

TABLE II

RELATIONSHIP BETWEEN THE CAUSE OF DEATH, MAXIMUM DEGREE OF NITROGEN RETENTION AND DURATION OF URINARY SUPPRESSION IN ELEVEN FATALITIES

Name	Age	Cause of Urinary Suppression	Cause of Death	N.P.N. B.U.N. (mg. %)	Days before Death	Duration of Suppression	Autopsy
G. M.	31	Ureteropelvic obstruction	Uremia	227	3	50 days	Ureteropelvic obstruction due to bilaterally aberrant renal arteries and veins
W. L.	55	Transfusion reaction	Pulmonary edema	150	0	12 days	Pulmonary edema, "hemoglobin nephrosis"
H. S.	51	Transfusion reaction	Generalized peritonitis following pancreatotomy	132	1	10 days	Generalized peritonitis, "hemoglobin nephrosis"
C. H.	79	Transfusion reaction	Sudden, unexplained	120	1	8 days	"Hemoglobin nephrosis," acute right pyelonephritis and acute cholecystitis
M. J.	63	Sulfadiazine nephrosis	Pulmonary emboli	96	2	8 days	Multiple pulmonary emboli and infarctions, sulfadiazine nephrosis
A. G.	62	Intravascular hemolysis due to sulfanilamide	Anemia, congestive failure and uremia	380	1	8 days	"Hemoglobin nephrosis," congestive cardiac failure
E. R.	53	Acute glomerulonephritis	Sudden, unexplained	145	1	7 days	Absent left kidney, acute glomerulonephritis, right
A. S.	24	Postpartum suppression	Sudden, unexplained	136	1	7 days	"Lower nephron nephrosis"
C. F.	86	Sulfathiazole nephrosis	Pneumonia, cardiac failure and uremia	190	1	7 days	Sulfathiazole crystals in tubules, ureter and bladder; bronchopneumonia, arteriosclerotic heart disease with congestive failure
R. B.	57	Shock, peritonitis, ileus	Generalized peritonitis after abdominal operation	104	2	6 days	None
M. T.	32	Postpartum suppression	Pulmonary edema	80	4	7 days	None

venous pressure elevation to 240 mm. of water following excessive fluid administration. The second instance was that of an eighty-six year old male who entered the

water. After seven days of hospitalization, during which time he was unconscious, the patient developed urinary suppression due to sulfathiazole administration. He died

seven days later with a serum non-protein nitrogen level of 190 mg. per cent. In the face of major extrarenal complications it would be incorrect to ascribe either of these two deaths to uremia alone.

Three patients died suddenly over a

potassium intoxication as the cause of death in these three instances. Postoperatively, one of these patients, a seventy-nine year old male, had a complicating acute cholecystitis and pyelonephritis at autopsy. In the other two patients no anatomic cause

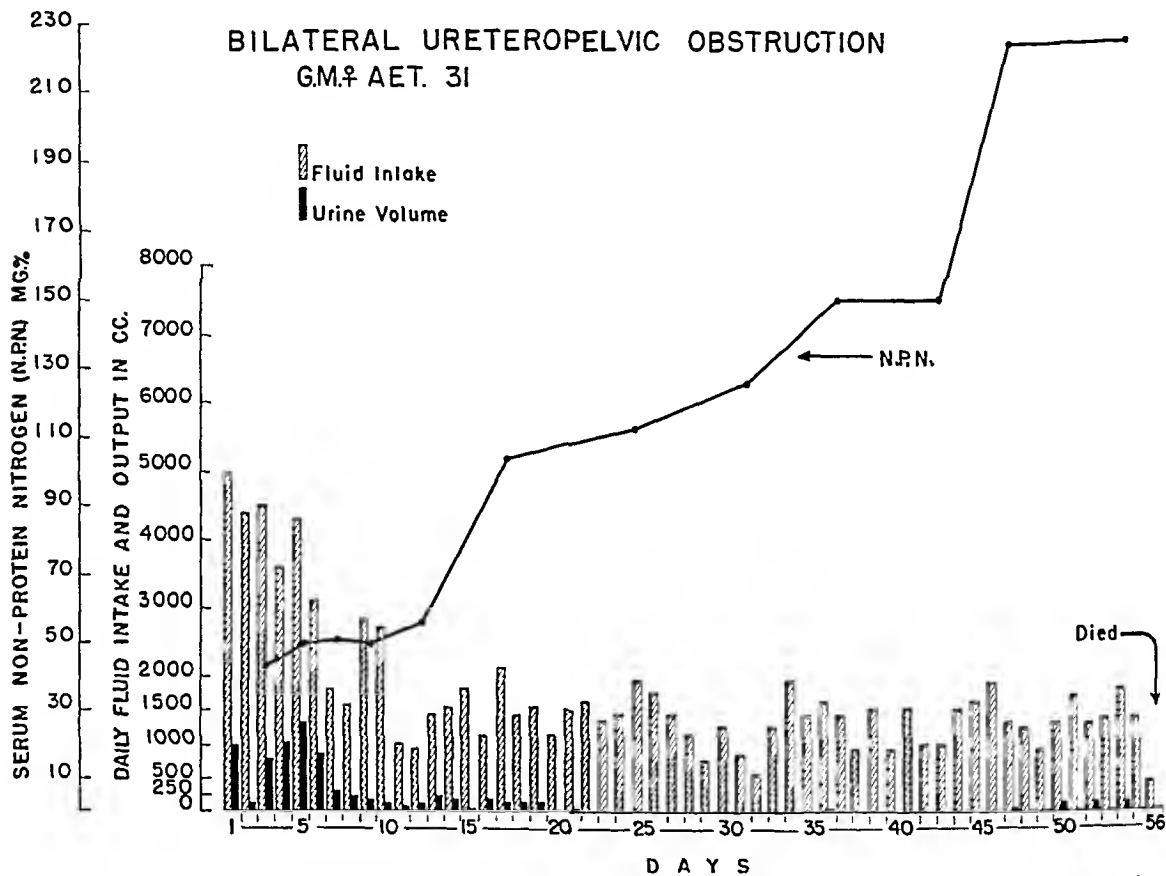


FIG. 2. This patient was admitted for investigation of extensive ankylosing rheumatoid arthritis and for regulation of diabetes mellitus in mild acidosis. She gradually developed progressive urinary suppression, azotemia and peripheral edema without other signs of circulatory failure or abnormalities of blood pressure. Ankylosis of both hips prevented cystoscopy. She was given no parenteral fluids and remained completely rational until two days before death. Autopsy examination identified congenitally aberrant renal arteries and veins bilaterally, producing complete ureteropelvic obstruction. The serum potassium was 5.7 mEq./L. prior to death.

period of several minutes to one hour with serum urea nitrogen levels of 120 and 145 mg. per cent and a non-protein nitrogen level of 136 mg. per cent, respectively. Immediately preceding death the clinical condition of each patient was thought to be satisfactory. The level of nitrogen retention in each instance was below the general average of nitrogen retention. Failure to take electrocardiographs and to obtain serum potassium levels prior to death precluded the possibility of establishing

for death was found at postmortem examination other than the renal lesion.

The last fatality, ending in uremia after fifty days of urinary suppression due to bilateral ureteropelvic obstruction, has been mentioned. (G. M., Fig. 2.) In all of the eleven surviving patients with so-called "lower nephron nephrosis" the early appearance of diuresis prevented urinary suppression of this duration from taking place. In each instance of urinary suppression in this series resulting from lower nephron

nephrosis diuresis occurred within sixteen days. In all instances death occurred before the twelfth day. (Table III.)

In summary, of eleven deaths five were due to pulmonary edema or to completely unrelated coexisting fatal diseases. Three

elderly patients died with uremia and severe cardiac failure, one complicated by pneumonia and the other by marked anemia. Only one death may be solely ascribed to uremia and this did not occur until after the fiftieth day of severe urinary suppression.

INTRAVASCULAR HEMOLYSIS DUE TO SULFANILAMIDE

A.G. ♂ A.E.T. 62

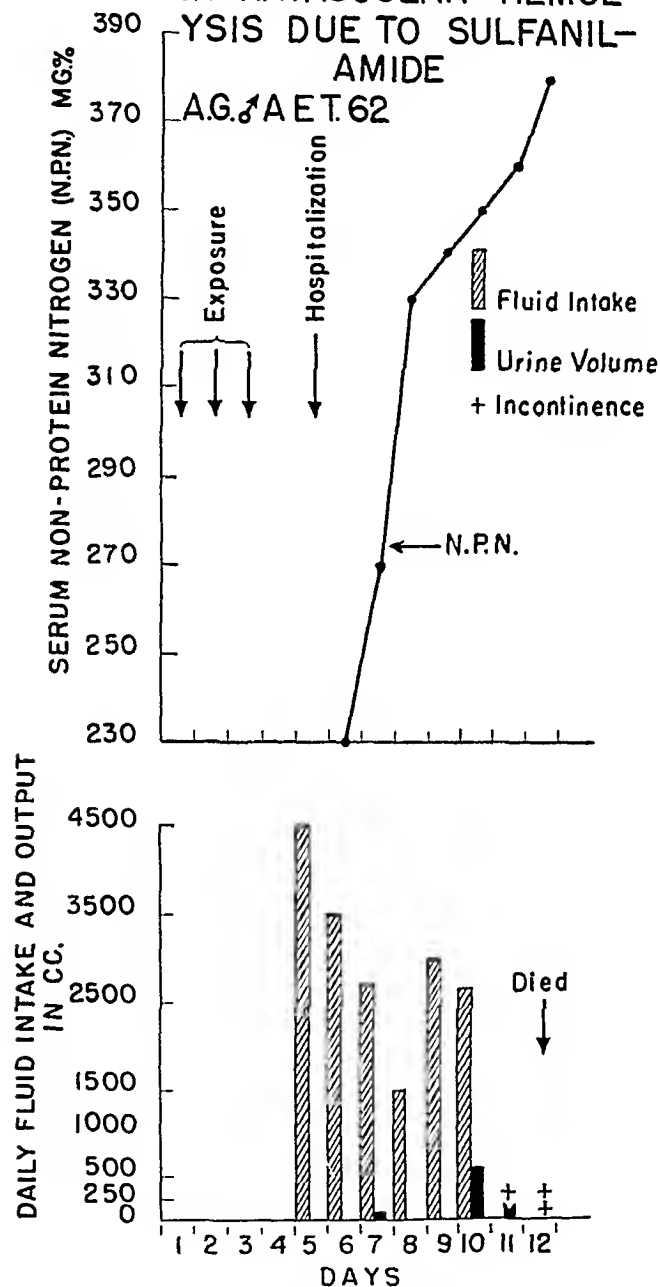


FIG. 3. This man was given oral sulfanilamide for a skin infection starting four days before admission. He developed a severe, acute hemolytic anemia ending fatally in urinary suppression. The excessively high level of serum N. P. N. probably resulted from massive blood destruction.

deaths occurred suddenly with degrees of nitrogen retention below the general average for surviving patients so that potassium intoxication may have played a role. Two

TABLE III
RELATIONSHIP BETWEEN MAXIMUM DEGREE OF NITROGEN RETENTION AND DURATION OF URINARY SUPPRESSION IN ELEVEN SURVIVING PATIENTS

Name	Age	Cause of Urinary Suppression	Maximum N P N. B.U N. (mg. %)	Duration of Suppression
I. W.	18	Diabetic acidosis with shock	122	15 days
E. S.	32	Mercury bichloride poisoning	206	14 days
H. B.	29	Transfusion reaction	225	13 days
H. Q.	36	Carbon tetrachloride poisoning	192	12 days
L. H.	39	Transfusion reaction	113	12 days
G. G.	31	Postpartum suppression	139	12 days
M. T.	38	Pentachloronaphthalene poisoning	142	10 days
H. B.	33	Bacitracin toxicity	127	10 days
E. L.	34	Transfusion reaction	129	8 days
F. H.	63	Diabetic acidosis with shock	150	7 days
R. W.	37	Carbon tetrachloride poisoning	94	6 days

The conclusion seems warranted that urinary suppression relatively infrequently causes death unless the patient's health is otherwise jeopardized. This is supported by comparison of the ages of the surviving and fatal groups:

Average age of the entire group (22 patients)	44 7 years
Average age of the 11 survivors.	35 4 years
Average age of the 11 fatalities	53 9 years

There were nine patients above the age of fifty. Of this group only one survived (89 per cent mortality). There were thirteen patients below the age of fifty. Of this group only three died (23 per cent mortality). The coexistence of underlying disease in the elderly with superimposition of urinary suppression accounted for most of the fatalities observed in that group.

CLINICAL FEATURES

Periorbital Edema. Of twenty-two patients, six had periorbital edema at a time when peripheral edema was slight or absent. Transfusion reaction and toxicity from

mercury, carbon tetrachloride and bacitracin accounted for the underlying disease.

Hypertension. Serial observations were made in all patients. Elevation of both the systolic and diastolic blood pressures above 140/90 occurred in thirteen instances. Hypertension was noted as early as the third day of urinary suppression and regularly subsided within twenty-six days. In three patients elevation of the blood pressure did not occur until after onset of diuresis.

Convulsions. Generalized convulsions in clonic and tonic phases were observed in five patients with and without associated hypertension. Three of these patients recovered.

Pericardial Friction Rub. A pericardial friction rub was noted in only one patient. This appeared on the twenty-third day of urinary suppression and persisted until death twenty-seven days later.

CHEMICAL STUDIES

Nitrogen Retention. Serial determinations of either the serum non-protein or urea nitrogen were made in every instance. No absolute correlation could be found between the duration of urinary suppression and the height of nitrogen retention. This might be expected as the rate of formation of non-protein nitrogen and its excretion varied tremendously from patient to patient. In the instance of A. G. (Fig. 3) excessive serum non-protein nitrogen formation, resulting from red blood cell destruction due to the hemolyzing effect of sulfanilamide, was reflected by a rapid rise in the serum non-protein nitrogen to a level of 380 mg. per cent on the eighth day of urinary suppression. On the other hand, considerable extrarenal excretion of nitrogen must have occurred in the instance of G. M. (Fig. 2), in whom the serum non-protein nitrogen reached a level of only 227 mg. per cent on the forty-seventh day of urinary suppression. In the latter instance the patient lost several hundred cc. of serous fluid daily from multiple subcutaneous blebs and needle puncture wounds. Ample amounts of this fluid were easily obtainable. Analysis on

one occasion disclosed that it contained 105 mg. per cent of non-protein nitrogen.

The general average of maximum serum urea nitrogen levels in the survivors was 155 mg. per cent. In the eleven fatalities only three attained levels higher than this whereas a serum urea nitrogen level of 225 mg. per cent, occurring in one surviving patient (H. B., Fig. 6), was greater than the highest value for nitrogen retention in all but one of the fatal cases. In most patients it was observed that the serum non-protein or urea nitrogen continued to mount during the early stages of diuresis.

Uric Acid. Retention of this substance paralleled that of the total non-protein nitrogen. Values as high as 20 mg. per cent were encountered.

Calcium and Phosphorus. Serial calcium and inorganic phosphorus determinations were made on nine patients. The degree of phosphorus accumulation and calcium depression tended to parallel that of the serum non-protein nitrogen. An increase in the serum inorganic phosphorus level to 12 mg. per cent and a reduction of serum calcium to 7 mg. per cent was encountered. Neither latent nor overt tetany was observed.

Sodium. Direct serum sodium determinations by flame photometry were made in only four instances. Values varied from 122 to 145 mEq./L. and seemed to be a reflection more of the sodium intake than of any other factor. Serum sodium levels could not be correlated with the onset of diuresis or the amount of clinical edema.

Potassium. Serial potassium determinations were performed in six patients, with mild elevation occurring in five. The highest value obtained was 7.4 mEq./L. Electrocardiographic tracings made in seven patients were available. Review of these records failed to disclose abnormalities that could be caused by only electrolyte disturbances. No data concerning potassium were available in any instance of sudden unexpected death.

Carbon Dioxide Content. The carbon dioxide content of the serum was determined serially in eleven patients. In the absence of

bicarbonate or lactate administration there was a consistent tendency for acidosis to occur, as reflected by a gradual decline in the serum carbon dioxide content. The magnitude of this fall was of the order of 20 volumes per cent, but in two patients levels

was, in part, the presumptive cause for the decline in the hematocrit and for the low plasma protein values observed in the sixteen patients measured. Because of the frequency of coexisting intravascular hemolysis in this series, the hematocrit was not

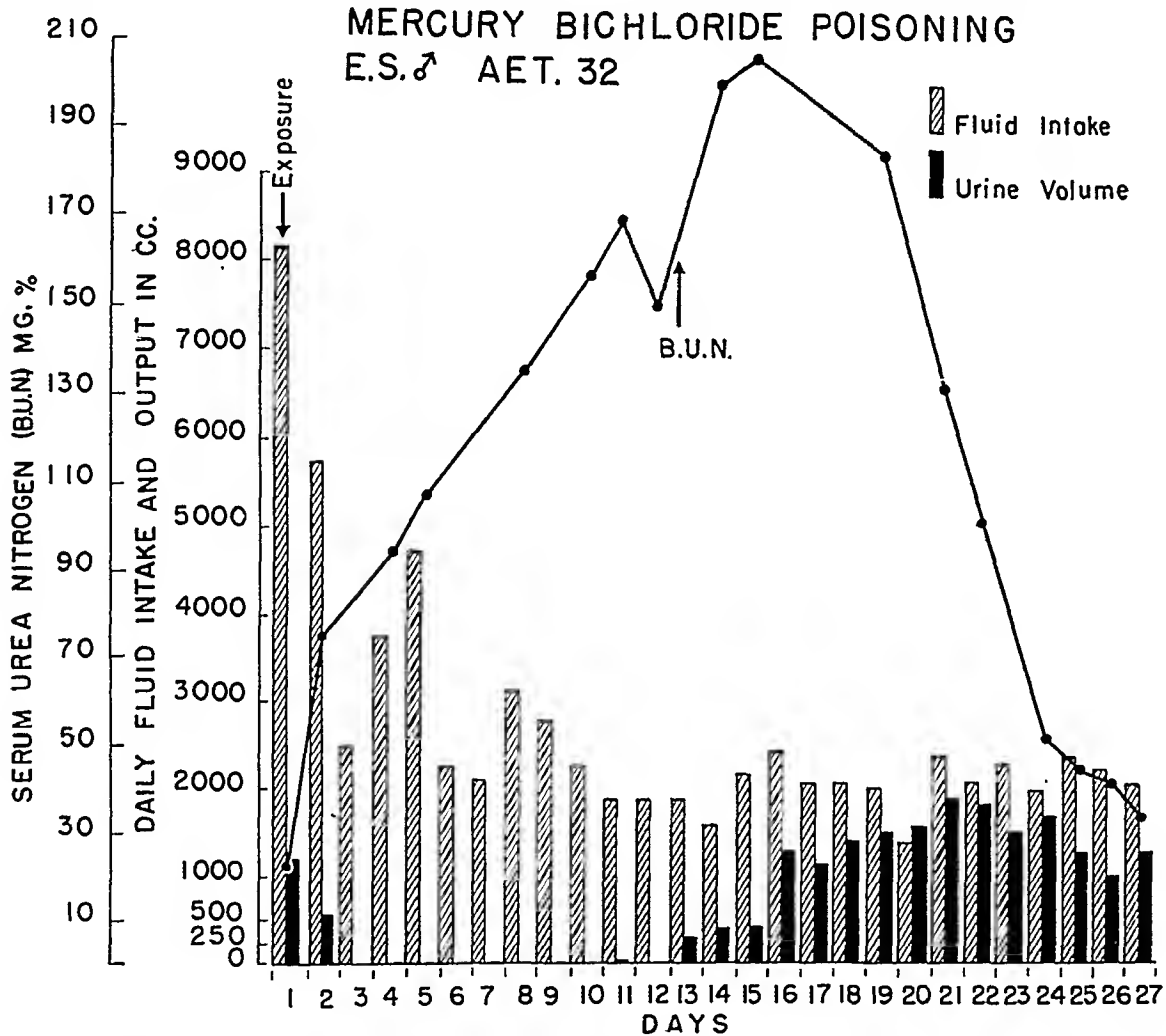


FIG. 4. This man consumed three tablets of mercury bichloride eight hours before admission and developed subsequent urinary suppression with complete recovery. He was given sodium thiosulfate daily. Mercury was identified in his urine.

of 17 and 18 volumes per cent were observed. As might be anticipated, administration of sodium chloride failed to correct this acidosis. Lactate and bicarbonate, on the other hand, produced a prompt elevation of the serum carbon dioxide content in each instance.

Chlorides. Serial determinations of the serum chlorides were made in ten patients. A general tendency to hypochloremia was observed, the lowest value being 77 mEq./L. Correction of the defect occurred promptly with administration of sodium chloride.

Hematocrit and Plasma Proteins. Hemodilution resulting from excessive fluid intake

always considered a reliable guide to further fluid therapy.

Fluid Balance. Of the twenty-two patients studied all except four developed peripheral edema. These four received an average fluid intake of 1,500 cc. daily in excess of measurable fluid loss. In three other patients administration of this same amount of fluid daily was associated with production of clinical edema. All of the remaining patients clearly received excessive fluids either parenterally or orally. All developed massive peripheral edema asso-

ciated with a 10 to 20 Kg. weight loss during the period of diuresis. (Fig. 4.)

Frank pulmonary edema due to excessive fluid administration was observed in three patients, resulting in two fatalities. A fluid intake of 2,000 to 3,000 cc. daily in excess

In the seven instances of urinary suppression due to intravascular hemolysis urinalysis was performed shortly after onset in six. In each of these six a guaiac test performed on the supernatant urine was strongly positive.

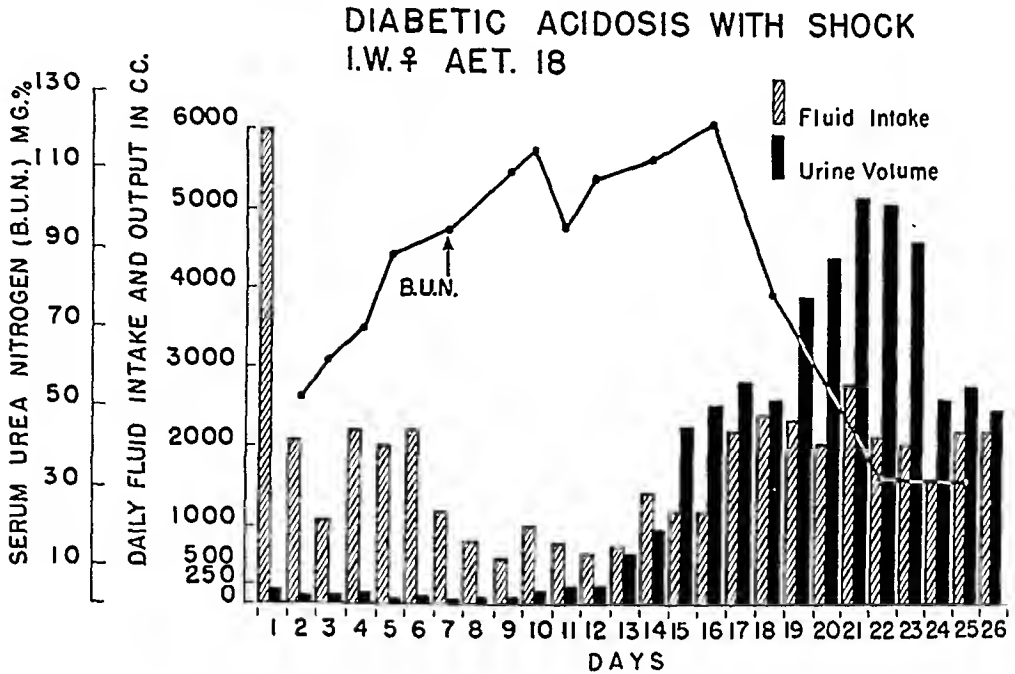


FIG. 5. This patient entered another hospital in marked diabetic acidosis and peripheral shock, responded well to routine treatment and was admitted two days later, at which time urinary suppression with peripheral edema was manifest. Her course was otherwise uncomplicated and recovery was complete.

of measurable fluid loss was found sufficient to produce this severe form of circulatory failure.

Venous pressures were measured in ten patients. Fluid in excess of 1,500 cc. was administered to nine of these patients, all of whom had unequivocal elevations of venous pressure, usually above 200 mm. of water.

Urine. Serial examinations of the urine were made in all twenty-two patients. Hyaline and granular casts were universally demonstrable but no other abnormalities were noted with this frequency. Red and white blood cells and albumin were present in almost all urines. Red blood cell casts were found only in association with acute glomerulonephritis. The specific gravity showed a tendency to fixation at 1.010 in almost all patients.

In both patients with diabetic acidosis it was observed that only minimal glycosuria and ketonuria were present despite demonstration of these substances in the serum in high concentrations. Similarly in all instances in which alkalization was attempted the scanty urine formed usually had an acid reaction to litmus paper despite serum carbon dioxide content levels of 70 to 80 volumes per cent. (Fig. 5.)

Treatment. The entire group was treated conservatively, with one exception. This patient (H. B., Fig. 6) had a transfusion with incompatible blood resulting in subsequent urinary suppression. On the ninth day a bilateral renal decapsulation was performed. Urinary output did not increase until the twelfth day, and 1,000 cc. of urine formation was not exceeded until the thirteenth day.

Postoperatively, a Miller-Abbott tube

was passed in two patients because of intestinal distention. In neither instance was the tube left in place for more than forty-eight hours, with total yields of 275 and 700 cc., respectively. Postoperatively, one patient who developed urinary suppression second-

Such treatment was not associated with diuresis in any instance.

In the remaining patients no attempts either to speed the onset of diuresis or create pathways for the extrarenal excretion of solutes was made. Treatment consisted of

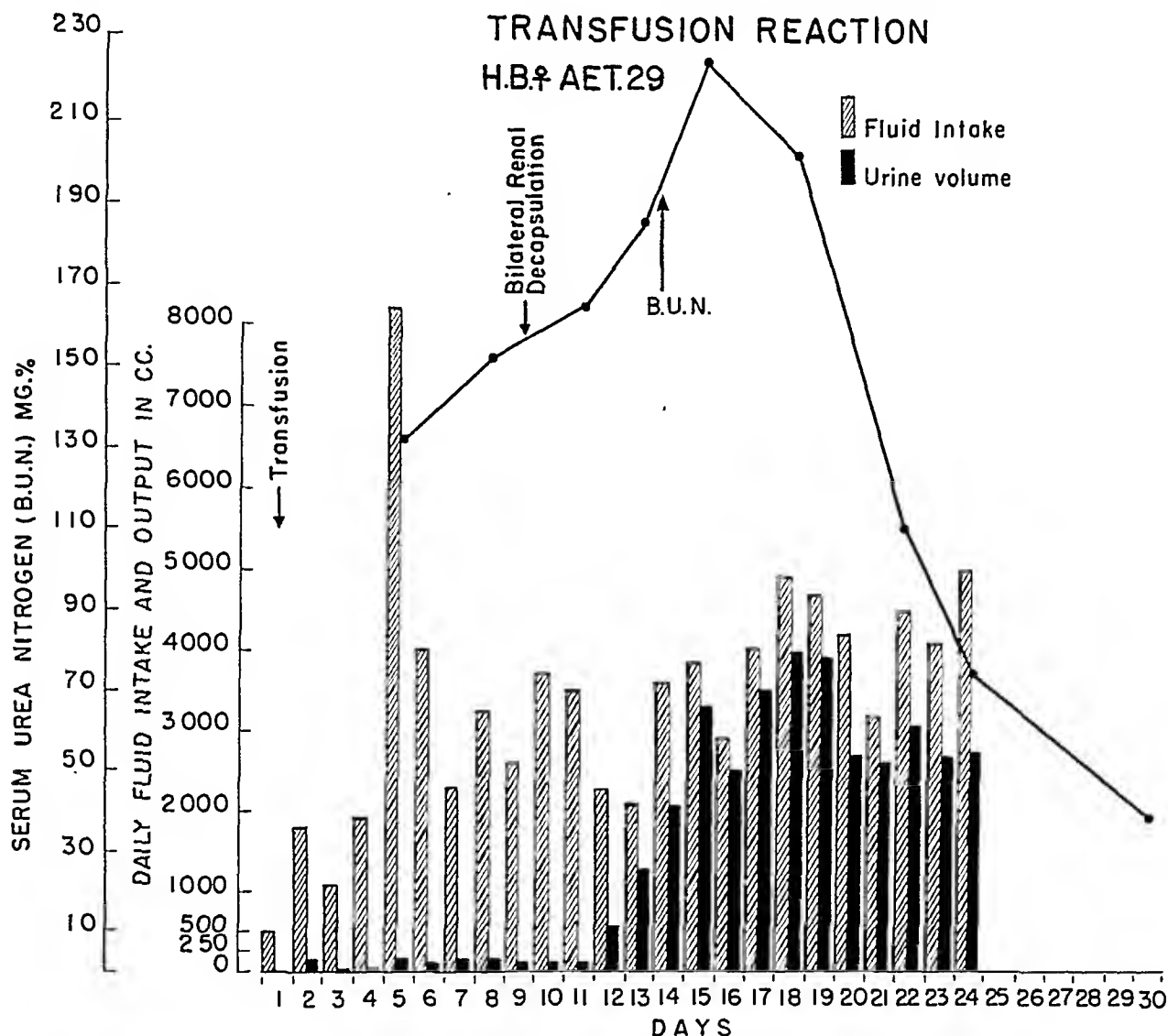


FIG. 6. This patient was admitted for uterine curettage and developed urinary suppression with complete recovery following a transfusion reaction. A bilateral renal decapsulation was not successful in initiating immediate diuresis. The diagnosis of "hemoglobin"nephrosis was substantiated by kidney biopsy.

ary to a transfusion reaction had a constant suction nasogastric tube in place throughout her course, with yields between 700 and 1,400 cc. daily. No definite effect on the serum non-protein or urea nitrogen level resulted from these inadequate attempts at gastrointestinal drainage.

The great majority of the twenty-two patients received intravenous injections of 50 per cent hypertonic glucose at some time during the period of urinary suppression.

general supportive measures according to the clinical situation and was not carried out in conformity with any over-all plan. (Fig. 7.)

Follow-up. Of the surviving eleven patients satisfactory follow-up examinations up to sixteen years were obtained in all but one instance. Normal values for blood pressure, urinalysis, serum urea nitrogen, ability to concentrate urine and phenolsulfonphthalein excretion were observed at the

end of two to three months and usually sooner.

COMMENTS

These observations have been presented in order to ascertain the natural history of

has outlined. Should retention of solutes occur in excess of the average values observed here, the cause must lie not with increased severity of renal disease but with either excessive solute consumption or with excessive breakdown of body tissue.

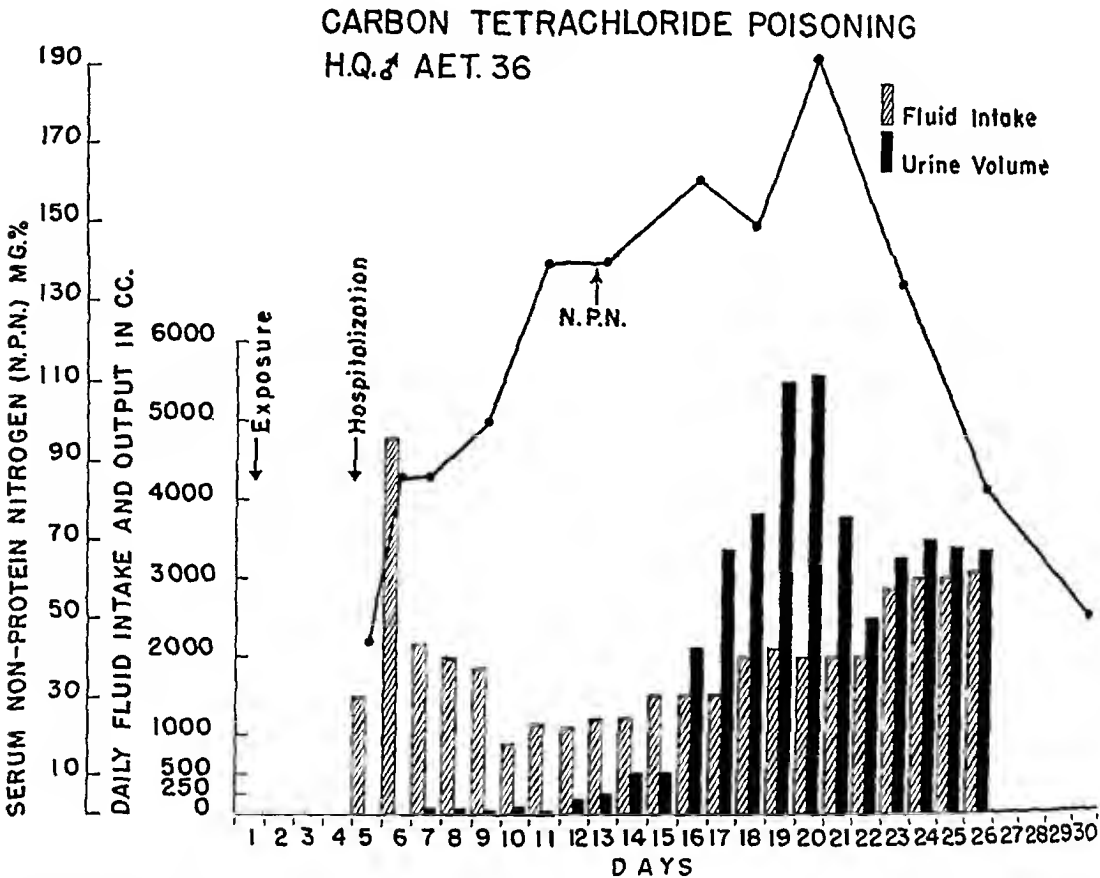


FIG. 7. This man inhaled the fumes of carbon tetrachloride in a closed room and developed subsequent urinary suppression three days before hospitalization. Frank pulmonary edema appeared during the early stages of diuresis but recovery was complete.

conservatively treated acute urinary suppression and to provide a control series for other methods of management currently advocated. The twenty-two patients described herein were selected as representing the maximum degree of suppression of urine formation and consequent loss of renal excretory function usually encountered clinically. Both from the standpoint of duration and magnitude of urinary suppression and from the degree of elevation of the serum non-protein or urea nitrogen, disease in these patients was of comparable severity to those treated by the methods Snapper¹

In this series approximately one-half of the deaths resulted directly from factors other than solute retention and could not have been prevented by any therapy directed at the alleviation of azotemia. In most of the remaining fatalities the retention of solutes was accompanied by severe co-existing physiologic disturbances in other systems of the body. Despite this fact the observed mortality rate of 50 per cent is considerably lower than the mortality rate for any published series thus far treated by the "artificial kidney," peritoneal dialysis, intestinal irrigation or exsanguinotrans-

fusion, as reviewed by Snapper.¹ It is clear, furthermore, that in one patient simple supportive measures were sufficient to sustain life for fifty days after the onset of severe urinary suppression although it should be added that seepage of edema fluid tended to ameliorate nitrogen retention. Several instances of similar long survivals have been reported in the literature and summarized by Strauss.⁴

In conclusion, analysis of the data presented herein indicates that urinary suppression is usually a self-limited disease when due to such causes as shock, intravascular hemolysis, postpartum eclampsia or poisoning by a variety of agents, including mercury bichloride. While diuresis occurs within two and one-half weeks in these conditions, life can be sustained without significant urine formation for a period of fifty days.

SUMMARY

1. Acute urinary suppression has been defined and observations recorded in a series of twenty-two patients exhibiting a measured urinary output of less than 100 cc. a day for three or more consecutive hospital days.

2. Twenty-one patients were treated conservatively without attempts either to speed the onset of diuresis or to create pathways for the extrarenal excretion of solutes. One patient underwent a bilateral renal decapsulation and diuresis occurred three days later.

3. Urinary suppression up to fifteen days' duration was associated with complete recovery in eleven patients.

4. Death ensued between the sixth and twelfth day of urinary suppression in ten instances.

5. The main causes of death as observed in this series were pulmonary edema resulting from excessive fluid administration and coexisting unrelated severe disease, such as generalized peritonitis and pulmonary embolism.

6. Urinary suppression of fifty days' duration was found compatible with life in one patient in whom bilateral ureteropelvic obstruction was demonstrable at autopsy. Seepage of edema fluid in this patient may have postponed exitus.

7. In the absence of severe coexisting disease, excessive fluid administration and unusually large amounts of tissue protein breakdown, spontaneous diuresis with complete recovery generally occurred. Consideration should be given to the usual favorable outcome of uncomplicated, conservatively treated, acute urinary suppression in evaluating the indications for and results obtained by the artificial kidney, peritoneal dialysis, intestinal irrigation, exsanguinotransfusion and similar procedures.

REFERENCES

1. SNAPPER, I. Management of acute renal failure. *Bull. New York Acad. Med.*, 25: 199, 1949.
2. CULPEPPER, W. S. and FINDLEY, T. Renal decapsulation for oliguria and anuria. *Am. J. M. Sc.*, 214: 100, 1947.
3. GAMBLE, J. L. Physiological information gained from studies on the life raft ration. The Harvy Lectures, 1946-47. P. 247. Lancaster, Pa., 1947. The Science Press Printing Co.
4. STRAUSS, M. B. Acute renal insufficiency due to lower nephron nephrosis. *New England J. Med.*, 239: 693, 1948.

Clinical and Metabolic Study of 11-Dehydro-17-hydroxy-corticosterone Acetate (Kendall Compound E) in Hypertension, Addison's Disease and Diabetes Mellitus*

GEORGE A. PERERA, M.D., KERMIT L. PINES, M.D., HOWARD B. HAMILTON, M.D. and
KATHERINE VISLOCKY
New York, New York

SINCE the isolation of 11-dehydro-17-hydroxy-corticosterone (Compound E of Kendall),¹ its administration has been associated with effects on protein and carbohydrate metabolism in both normal and adrenalectomized animals.²⁻⁸ These studies have in general revealed weight loss, suppression of growth, glycosuria, hyperglycemia with altered glucose tolerance, increased nitrogen excretion, increased urinary excretion of sodium and chloride, and sometimes ketonuria. Thorn and his associates have reported improvement in carbohydrate metabolism in patients with Addison's disease.^{9,10}

The present study was undertaken in order to determine the clinical and metabolic effects of synthetic 11-dehydro-17-hydroxy-corticosterone acetate administered to human subjects. Because of the possibility that this steroid might depress the arterial tension¹¹ in addition to its apparent effects on carbohydrate metabolism, observations were made on two patients with uncomplicated hypertensive vascular disease, one with Addison's disease and one with diabetes mellitus and hypertensive vascular disease.

CASE REPORTS

CASE 1. C. Z., a forty-three year old woman, was admitted to the metabolism ward of the Presbyterian Hospital because of dizziness, headaches and hypertension known for six years. There was neither past nor present evidence of cardiac pain, congestive failure, or renal, cerebral or obvious endocrine disease. Physical examination was not remarkable except for a blood pressure of 220/130, marked arteriolar narrowing and arteriovenous compression on funduscopic examination, and cardiac enlargement with a faint apical systolic murmur.

The patient was afebrile throughout the period of observation. Complete blood count, circulation time and venous pressure were within normal limits. Popliteal arterial pressures were not reduced. X-ray of the heart disclosed moderate hypertrophy, chiefly of the left ventricle, but the electrocardiogram showed no significant abnormalities. Repeated urinalyses were negative; the urine concentrated to a specific gravity of 1.024; the phenolsulfonphthalein excretion was 70 per cent in two hours; and the intravenous pyelogram was normal. A benzodioxane test¹² did not suggest the presence of a pheochromocytoma.

The patient was kept in bed until after blood studies and blood pressure measurements were

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University and The Presbyterian Hospital in the City of New York. This investigation was supported (in part) by a research grant from the National Heart Institute, U.S. Public Health Service, and was aided through the generosity of the Albert and Mary Lasker Foundation.

made, and ambulatory activity was standardized at a constant level the rest of the day. She was weighed daily before breakfast on the same scales. Distilled water was supplied for drinking. "Resting" blood pressures were measured each morning in the same arm by the same observer,

Sodium chloride was administered in constant amounts using weighed salt shakers.

After the preliminary period the patient was started on two baseline periods (I and II) of four days each. During a third and fourth four-day period (III and IV) she received 20 mg. of 11-

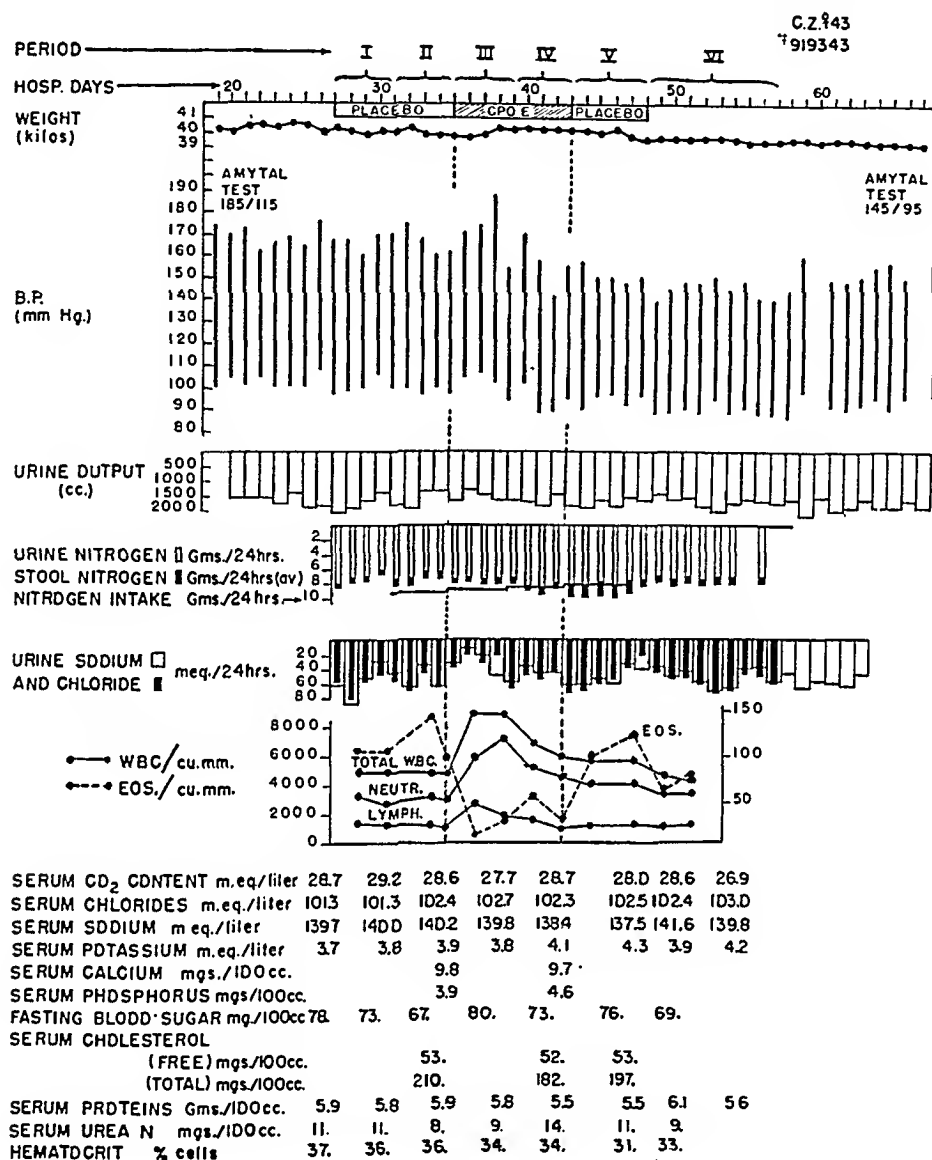


FIG. 1

with the subject quiet and relaxed in bed, the head of which was raised to a 30 degree angle. At least seven readings were taken at half-minute intervals and the lowest systolic and lowest diastolic values recorded. In order to secure an adequate baseline preliminary observations were carried out for twenty-seven days.

Throughout the study the patient was given a constant diet and fluid intake. Identical salt-poor daily menus (1,740 calories, including 50 Gm. of protein and 273 Gm. of carbohydrate) were prepared, the entire daily diet being subjected at intervals to direct chemical analysis.

dehydro-17-hydroxy-corticosterone acetate intramuscularly at six-hour intervals. Final periods (v and vi) of five and ten days, respectively, served as post-treatment controls. Placebo intramuscular injections (1 cc. of 5 per cent glucose) were given during periods I, II and V.

Intravenous glucose tolerance tests were performed by administering 0.5 Gm. of glucose per Kg. of body weight in 200 cc. of distilled water over a thirty-minute period.⁹ On the day of these tests the diet was reduced by amounts of glucose and drinking water equivalent to those employed in the procedure and breakfast was

held until the completion of the test. Sodium and potassium determinations were made with an internal standard flame photometer having an accuracy of ± 1 per cent. The nitrogen in the diet, urine and stool specimens was determined

method of Daughaday and co-workers.¹⁴ White blood cells were counted in duplicate using standard technic, and eosinophiles* counted according to the method of Thorn and his associates.¹⁵

TABLE 1(a)

Period	Hos- pital Day	Intake					Urine								Stool												
		Fluid	Na	Cl	K	N	Vol- ume	Na	Cl	K	N	17-keto- steroids	"Cor- ticoids"	Na	Cl	K	N										
		Cc.	mEq./24 hr.			Gm./ 24 hr.	Cc.	mEq.			Gm.	Mg./24 hr. (av.)	Mg.	mEq./24 hr. (av.)			Gm/ 24 hr (av.)										
I	27	2,250					2,130	60	5	59	5	67	3	8	14		2	88									
	28	2,250					1,940	85	7	80	3	59	4	7	38		2	30									
	29	2,250					1,720	52	3	56	3	51	9	7	07	7	03	2	13	2	7	0	9	7	2	0	75
	30	2,250					1,380	27	2	46	8	56	3	6	16		1	62									
II	31	2,250					1,810	43	4	55	3	73	8	7	76		1	98									
	32	2,250					1,980	62	8	69	2	63	7	7	34		2	61									
	33	2,250	58	9	62	5	66	7	9	34						10	66	1	79	4	3	1	6	10	0	1	07
	34	2,250					1,310	62	4	63	9	57	4	6	46		1	94									
III Compound E	35	2,250					1,660	33	1	37	0	72	4	7	52		2	10									
	36	2,250					1,290	11	0	19	7	43	5	7	36	6	37	1	49								
	37	2,250	59	4	60	9	63	2	8	92							1	61	1	4	0	7	6	1	0	65	
	38	2,250					1,630	46	1	21	9	53	1	7	51	5	56	2	33								
IV Compound E	39	2,250					1,640	57	8	66	8	50	9	7	48		4	78									
	40	2,250					1,690	34	0	47	1	57	8	8	35	5	40	2	56								
	41	2,250	58	9	60	3	62	2	8	68							2	94	2	8	1	0	8	5	0	79	
	42	2,250					1,460	46	0	46	6	40	6	8	03	7	55	1	39								
V	43	2,250					1,790	62	3	72	6	48	8	8	22		0	95									
	44	2,250					1,840	60	3	67	2	58	2	8	24	4	36	1	81								
	45	2,250	57	8	61	8	63	4	8	30							1	91	2	5	1	3	6	8	1	79	
	46	2,250					1,800	58	3	56	0	73	8	8	10	4	57	1	16								
	47	2,250					1,560	34	0	37	9	57	0	7	63												
																6	14										
VI	48	2,250					1,620	40	5	40	7	68	0	7	74		1	67									
	49	2,250					1,490	36	1	45	3	59	0	7	02		1	28									
	50	2,250					1,690	48	0	53	4	60	0	7	57	6	54	0	89	3	0	1	4	7	6	0	70
	51	2,250					1,650	41	3	52	5	65	3	7	29												
	52	2,250					1,800	55	4	57	6	65	9	7	54		2	08									
	53	2,250					2,010	74	8	76	2	63	7	7	44	6	95	2	09								
	54	2,250					1,760	67	8	70	7	62	0	7	42												
	55	2,250					1,620	38	1	47	6	57	4				1	56									
	56	2,250					1,650	36	8	49	5	57	6	7	24												
	57	2,250					1,700	56	4	57	6	55	6				1	23									

by micro-Kjeldahl procedures. The stools for each experimental period were collected as a single specimen. 17-ketosteroids were estimated by a modification of the method of Callow, Callow and Emmens¹³ and "corticoids" by the

Results. The results are shown in Figure 1 and Table 1. No subjective change was

*We are indebted to Mr. Paul Marks and Mrs Dorothy Marks for these determinations.

noted. Compound E in the dosage employed (80 mg. daily) appeared to have a small but definite effect on water and salt metabolism. The weight increased; there was a suggestive decrease in urine volume

Nitrogen balance studies indicated an increased excretion appearing only after five days of treatment and persisting for about the same period after the administration of Compound E had been discontinued.

TABLE I(b)

Period	Hos- pital Day	Weight	"Rest- ing" B.P.	Sed. Rate	Hemato- crit	W.B.C.	Neutro- phils	Lympho- cytes	Eosino- philes	Blood Sugar and Glucose Tolerancce					
										Fast- ing	½ Hr.	1	2	3	4
		Kg.	Mm. Hg	Mm./ hr.	% Cells	Cells/cu.mm.				Mg./100 cc.					
I	27	40.29	166/96	..	37	78					
	28	40.00	166/98	4,700	3,102	1,316	112						
	29	39.95	160/100										
	30	40.05	170/106	6	..	4,300	2,666	1,311	111	73	154	103	77	80	85
II	31	40.05	170/100	..	36										
	32	40.25	174/100										
	33	39.86	166/96	4,700	3,219	1,199	147						
	34	39.95	160/100	4,020	2,934	1,060	77	67	121	93	71	61	80
III Com- pound E	35	39.80	162/96	..	36										
	36	39.65	170/104	8,880	5,683	2,664	12						
	37	39.95	174/106										
	38	40.27	188/102	8,900	7,120	1,691	27	80	182	121	74	79	93
IV Com- pound E	39	40.20	154/94	..	34										
	40	40.25	170/102	6,900	5,106	1,518	59						
	41	40.24	156/88										
	42	40.26	140/88	5,820	4,598	931	25	73	154	97	58	75	68
V	43	40.25	154/94	7	34										
	44	40.13	156/92	5,480	4,000	1,205	90						
	45	40.00	148/96										
	46	40.30	150/96										
	47	39.90	146/92	5,500	4,015	1,330	125	76	154	85	60	64	74
VI	48	39.64	152/96	5	31										
	49	39.66	140/88	4,600	3,312	1,012	61						
	50	39.74	144/88										
	51	39.67	146/90	..	33	4,550	3,253	1,229	81	69	167	83			
	52	39.78	146/88										
	53	39.82	150/94										
	54	39.62	144/88										
	55	39.39	148/90										
	56	39.56	140/88										

and a definite decrease in urinary sodium and chloride; and evidence of hemodilution was obtained by changes in hematocrit and protein values.

Although a slight decrease in serum sodium and a suggestive increase in serum potassium concentrations were noted, serum electrolyte and calcium values were not

materially affected. There was an increase in the concentration of serum inorganic phosphorus. A slight decrease in total cholesterol was observed which was not at the expense of the free fraction. Urinary 17-ketosteroid and "corticoid" excretion did

teleroentgenograms and serial electrocardiograms were not modified.

A transitory increase in total white cell count, due primarily to a rise in polymorphonuclear leukocytes, immediately followed the use of Compound E, together with a sharp but more sustained drop in eosinophiles.

The "resting" blood pressure, after an initial rise, began to fall after the first period of steroid administration and remained at lower values throughout the post-treatment observation.

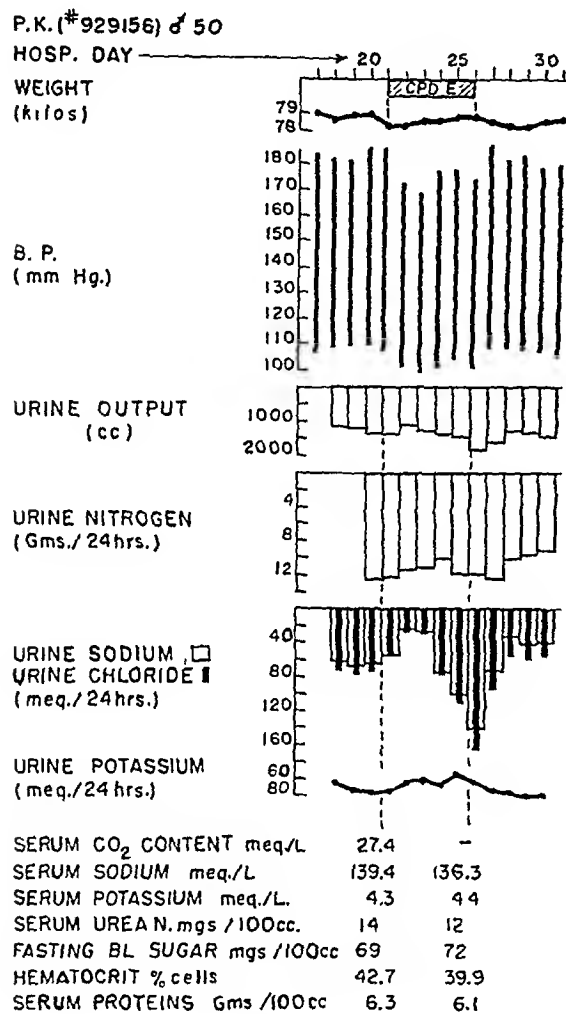


FIG. 2

not change to a great extent. On the fourth day of treatment the fasting and peak levels of blood sugar were higher than in other glucose tolerance tests but the results were of doubtful significance. The urine was analyzed daily for reducing substances, acetone and diacetic acid. All samples were negative with the exception of that obtained on the fourth day of treatment in which a trace of acetone was disclosed. The sedimentation rate remained unaltered and

CASE II. P. K., a fifty year old laborer, was admitted because of heart consciousness, fatigue on exertion and hypertension of six months' known duration. Physical examination was normal save for a blood pressure of 235/140, moderate arteriolar thickening and arteriovenous compression on fundoscopic examination and cardiac enlargement without murmurs. There was neither past nor present evidence of cardiac pain, congestive failure, or renal, cerebral or obvious endocrine disease.

The patient was afebrile throughout the period of observation. Complete blood count, circulation time and venous pressure were within normal limits. Popliteal artery pressures were not reduced. X-ray of the heart disclosed moderate cardiac hypertrophy; the electrocardiogram showed left axis deviation, a diphasic T wave in the first lead and inversion of the T wave in lead CF₄. Repeated urinalyses were negative; the urine concentrated to a specific gravity of 1.024; the phenolsulfonphthalein excretion was 50 per cent in two hours; and an x-ray of the renal area revealed the kidney shadows to be normal in size, shape and position with no evidence of calculi. A benzodioxane test was negative.

The conditions of the experiment were identical to those previously described except that Compound E (20 mg. intramuscularly at six-hour intervals) was administered for five days, beginning on the twenty-first hospital day, and less extensive studies were undertaken. The diet employed in this patient contained 2,175 calories per day which included 85 Gm. of protein and 267 Gm. of carbohydrate.

Results. The results are shown in Figure 2 and Table II. No subjective change was

noted. Compound E (80 mg. daily) appeared to have a small effect on water and a definite effect on salt metabolism. The weight increased slightly. There was a transitory small decrease in urine volume and a more marked retention of sodium

of steroid administration (at the same time as salt and water retention was observed) but returned promptly to baseline levels.

CASE III. J. R., a thirty-four year old, white clerk, had been in good health until seven years before the present study. At that time he de-

TABLE II

Period	Hos- pital Day	Weight Kg.	"Resting" B.P. Mm. Hg	Intake			Urine				
				Fluid	Na	N	Volume	Na	Cl	K	N
				Cc.	mEq.	Gm.	Cc.	mEq.			Gm.
I	17	78.85	184/106	1790	83.8	13.5					
	18	78.40	182/108	1790	83.8	13.5	1,210	62.6	71.5	65.3	
	19	78.89	182/110	1790	83.8	13.5	1,270	66.8	78.2	73.2	
	20	78.85	184/110	1790	83.8	13.5	1,370	64.4	74.9	78.4	12.7
II Compound E	21	78.25	184/106	1790	83.8	13.5	1,360	55.6	56.3	76.7	12.4
	22	78.20	172/102	1790	83.8	13.5	1,170	24.2	27.3	65.3	11.7
	23	78.50	170/100	1790	83.8	13.5	1,280	26.9	27.4	61.7	11.3
	24	78.60	178/102	1790	83.8	13.5	1,350	75.4	78.5	67.5	10.1
	25	78.85	178/104	1790	83.8	13.5	1,440	102.7	111.4	56.9	12.0
III	26	78.80	184/102	1790	83.8	13.5	1,850	143.8	166.0	63.9	12.0
	27	78.50	188/110	1790	83.8	13.5	1,600	74.2	92.6	76.4	12.6
	28	78.20	182/110	1790	83.8	13.5	1,240	34.5	57.9	77.4	10.1
	29	78.20	182/108	1790	83.8	13.5	1,300	45.7	59.1	82.2	9.7
	30	78.45	178/108	1790	83.8	13.5	1,450	43.8	57.7	79.4	
	31	78.60	180/106	1790	83.8	13.5	1,400	38.6	58.8	66.8	

and chloride during the first few days of drug administration. This was followed by a pronounced sodium and chloride (and to a lesser extent water) diuresis which began before the steroid was discontinued. Serum protein, hematocrit and urea nitrogen values suggested slight hemodilution.

Although nitrogen studies were limited to estimations of urinary excretion, the dietary intake being constant, no significant changes took place. There was a decrease in the serum sodium concentration. Fasting blood sugar values were not materially affected in this study. No glycosuria was produced but again a trace of acetone appeared in the urine on the fourth day of steroid treatment.

The "resting" blood pressure, which had fluctuated only from 180 to 190 systolic and 106 to 110 diastolic for several weeks before Compound E, fell slightly during the period

veloped weakness, fatigue, hypotension, nausea, skin and buccal mucous membrane pigmentation, and subsequently experienced several episodes suggestive of hypoglycemic reactions. The diagnosis of Addison's disease was clinically apparent and was substantiated by the finding of repeated serum sodium values which were markedly below normal limits. He was maintained in normal electrolyte and water balance by the subcutaneous injection of 2 mg. of desoxycorticosterone acetate* daily as well as by the addition to his regular diet of varying amounts of sodium chloride.

On this admission, except for the characteristic pigmentation and hypotension there were no abnormal physical findings. X-ray of the lungs and adrenal areas showed no signs of tuberculosis or abnormal calcification; the erythrocyte sedimentation rate was within nor-

* Furnished through the courtesy of Dr. K. W. Thompson of Roche-Organon, Inc., Nutley, N. J.

mal limits; and repeated urinalyses showed no abnormalities.

Throughout the study the patient was maintained on 2 mg. of desoxycorticosterone acetate subcutaneously each day and 8 Gm. of sodium chloride added to his identical salt-poor daily

muscularly at six-hour intervals) was limited to five days (period v).

Glucose tolerance tests were conducted as previously outlined, with the diet being reduced by amounts of glucose and drinking water equivalent to those employed in the procedure.

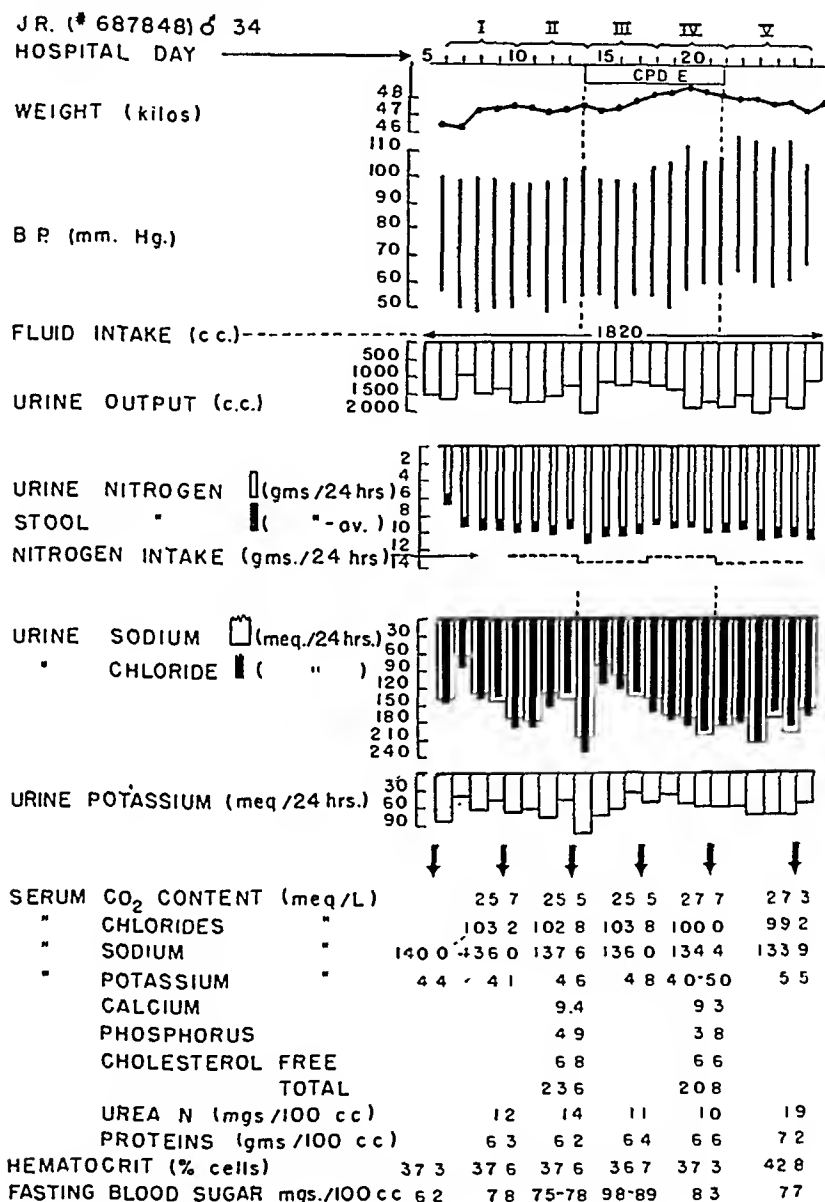


FIG. 3

menus. The daily diet contained 2,220 calories which included 75 Gm. of protein and 228 Gm. of carbohydrate. The conditions of the experiment were exactly the same as those described in the first patient except that period 1 began on the sixth hospital day and the length of observation after Compound E (20 mg. intra-

By finishing the previous day's diet at an earlier hour, all glucose tolerance tests began after a seventeen-hour period of fasting.

Results. The results are shown in Figure 3 and Table III. No subjective change was noted except for the development of moder-

ate insomnia. Compound E (80 mg. daily) appeared to have a definite effect on water and salt metabolism. There was a transitory increase in the excretion of water, sodium, chloride and potassium during the first twenty-four hours of steroid administration.

tained throughout the experiment with no apparent modification.

The serum sodium concentration began to fall toward the end of the period during which the patient received Compound E and continued to fall to subnormal levels

TABLE III(a)

Period	Hos- pital Day	Intake					Urine							Stools			
		Fluid	Na	Cl	K	N	Vol- ume	Na	Cl	K	N	17-keto- steroids	"Corti- coids"	Na	K	N	Fat
		Cc.	mEq./24 hr.			Gm./ 24 hr.	Cc.	mEq.			Gm.	Mg./24 hr. (av.)		mEq./ 24 hr. (av.)		Gm./24 hr. (av.)	
I	6	1,820	1,660	139.1	158.8	82.8	5.56						
	7	1,820	880	63.7	84.4	41.5	8.40						
	8	1,820	1,490	129.6	140.8	64.7	8.97						
	9	1,820	1,340	143.3	138.3	44.8	8.72	8.10	0.14	2.6	6.9	1.03	2.59
II	10	1,820					1,730	173.2	195.5	66.8	9.06						
	11	1,820					1,760	178.8	191.3	61.1	8.73			2.4	5.6	.96	2.85
	12	1,820	166.2	168.0	78.6	12.74	1,580	134.0	155.3	78.7	9.27	6.45	0.23				
	13	1,820					1,250	141.0	130.0	48.5	8.45						
III Com- pound E	14	1,820					2,040	209.7	235.9	106.8	10.28						
	15	1,820					1,200	82.2	118.3	73.7	9.70	7.00	0.52				
	16	1,820	166.4	168.1	80.8	13.40	1,320	100.6	123.8	62.8	9.40			6.2	8.3	1.10	2.48
	17	1,820					1,270	138.4	131.6	34.4	9.18	6.82	0.32				
IV Com- pound E	18	1,820					1,130	142.1	165.5	51.5	8.30						
	19	1,820					1,340	170.2	179.8	35.8	8.95	6.69	0.38				
	20	1,820	165.5	167.1	78.9	12.96	1,810	177.7	186.8	53.2	8.92			0.7	2.9	.43	1.26
	21	1,820					1,610	207.0	205.0	60.1	9.68	7.35	0.66				
V	22	1,820					1,700	186.3	188.7	59.5	9.09						
	23	1,820					1,510	174.2	182.7	60.4	8.60	6.31	0.46				
	24	1,820	165.0	168.5	83.4	13.70	2,010	220.4	220.4	76.2	9.90			1.1	6.1	1.09	3.60
	25	1,820					1,650	179.6	166.9	74.9	9.44	6.45	0.51				
	26	1,820					1,870	200.8	190.7	75.7	9.54						
	27	1,820					1,160	160.8	169.5	56.1	9.97	6.13	0.48				
													0.51				

This, however, was followed by an increase in weight, a decrease in urine volume, urinary sodium and chloride for several additional days only. Significant changes in hematocrit and serum protein levels did not develop but the serum urea nitrogen concentration decreased slightly.

A positive nitrogen balance was main-
JULY, 1949

during the final control period. There were reciprocal changes in serum potassium. As this subject developed twenty-four hours of generalized aches and slight fever the day following the conclusion of the final control period, it is not clear whether this alteration was related to the diuresis which commenced before the steroid was discontinued

or represented a metabolic change relating to the prodromas of an illness.

Compound E administration was associated with a fall in serum inorganic phosphorus concentration, again a slight decrease in total cholesterol, but no major change in

tolerance tests were uniformly conducted after a seventeen-hour fasting period. Daily analyses of the urine for reducing substances or ketone bodies were negative.

Determinations of radioactive iodine uptake,¹⁷ after the administration of 40 micro-

TABLE III(b)

Period	Hospital Day	Weight	"Resting" B.P.	E.S.R.	Hematocrit	W.B.C.	Neutrophils	Lymphocytes	Eosinophiles	Blood Sugar and Glucose Tolerance					
										Fast-ing	½ Hr.	1	2	3	4
		Kg.	Mm. Hg	Mm./hr.	% Cells	Cells/cu. mm.				Mg./100 cc.					
I	6	46.50	100/56	10	37.3	8,980	1,976	5,747	625	62					
	7	46.40	98/50												
	8	47.25	100/48												
	9	47.35	100/50	7,500	1,950	4,837	733	78	211	136	68	80	67
II	10	47.70	98/50	..	37.6										
	11	47.50	98/54												
	12	47.25	98/48												
	13	47.40	100/52	7,700	2,156	4,774	859	78	220	127	61	55	58
III Compound E	14	47.60	104/54	..	37.6	75					
	15	47.30	100/54												
	16	47.55	100/50												
	17	47.95	98/54	10,720	6,914	3,538	281	98	200	132	83	..	83
IV Compound E	18	48.20	104/54	..	36.7	89					
	19	48.45	106/50												
	20	48.80	112/56												
	21	48.55	106/60	10,535	7,322	2,844	234	83	200	147	69	76	81
V	22	48.20	108/60	15	37.3										
	23	48.05	116/64												
	24	48.10	114/60												
	25	47.70	112/58												
	26	47.85	114/60												
	27	47.30	104/66	..	42.8	77	250	132	80		
	33					7,700	2,926	3,927	806						

urinary 17-ketosteroid or "corticoid" excretion. The total stool fat¹⁶ was not modified significantly.

On the fourth and fifth day of treatment the fasting blood sugar levels were slightly higher than in other tests, and the blood sugar curves after intravenous glucose were minimally altered. No hypoglycemic reactions occurred at any time even though the

curies, were carried out eight days apart at the end of period II and IV; the uptake measured at twenty-four hours decreased from 23 to 14 per cent. The cardiac silhouette by x-ray increased very slightly following Compound E, and a slight elevation in the T waves was observed by electrocardiogram.

The "resting" blood pressure began to

rise after a few days of Compound E administration, peak values being reached just after the drug was discontinued.

CASE IV. M. S., a forty-six year old housewife, complained only of nervousness and weak-

were not reduced. X-ray of the heart disclosed moderate hypertrophy and the electrocardiogram showed left axis deviation and myocardial damage. Repeated urinalyses revealed variable glycosuria and two-plus albuminuria, together with occasional white blood cells; the urine con-

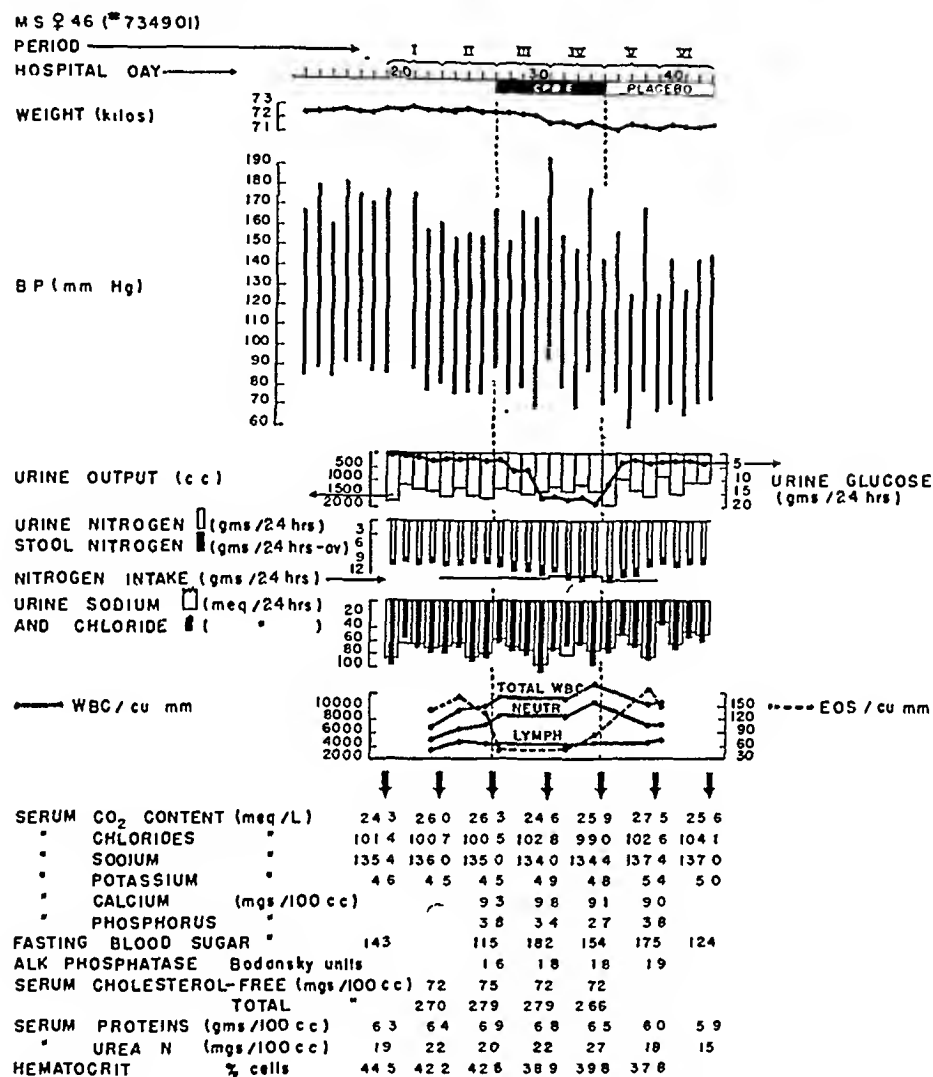


FIG. 4

ness when she was admitted after twenty-six years of known hypertension. Glycosuria with a fasting blood sugar of 152 mg. per 100 cc. was first noted five years before, initially controlled by diet alone and later supplemented by small doses of standard insulin. There was neither past nor present evidence of cardiac pain, congestive failure, cerebral disease or Cushing's syndrome. Physical examination was not remarkable except for a blood pressure of 230/110 and marked arteriolar changes, hemorrhages and exudate on fundoscopic examination.

The patient was afebrile throughout the period of observation. Complete blood count, circulation time and venous pressure were within normal limits. Popliteal arterial pressures

centrated to a specific gravity of 1.015; the phenolsulfonphthalein excretion was 80 per cent in two hours; and the intravenous pyelogram was normal. A benzodioxane test was negative.

The conditions of the experiment were identical with those described in the first patient. The diabetes was controlled satisfactorily with five units of standard insulin given daily before breakfast and at no time were there signs of acidosis, ketosis or insulin shock. No insulin was administered until the completion of the glucose tolerance test on the day when this procedure was undertaken. The diet employed in this patient contained 1,724 calories per day which included 70 Gm. of protein and 200 Gm. of

carbohydrate. Period I began on the nineteenth hospital day and Compound E (20 mg. intramuscularly at six-hour intervals) was administered for eight days. Placebo injections were given only during periods v and vi. The twenty-

dilution suggested slight retention. However, the urea nitrogen concentration rose during the periods of treatment.

Nitrogen balance studies indicated an increased excretion appearing soon after treat-

TABLE IV(a)

Period	Hos- pital	Intake					Urine								Stools			
		Fluid	Na	Cl	K	N	Vol- ume	Na	Cl	K	N	17-keto- steroids	"Corti- coids"	Na	K	N	Fat	
		Cc.	mEq./24 hr.			Gm./ 24 hr.	Cc.	mEq.			Gm.	Mg./ 24 hr. (av.)		mEq./ 24 hr. (av.)		Gm./24 hr. (av.)		
I	19	1,690	1,670	87.2	99.0	66.8	9.16	2.15	0.77	4.4	9.8	0.98	3.0	
	20	1,690	1,160	52.0	59.2	54.2	8.28							
	21	1,690	1,370	63.3	69.9	56.2	8.99							
	22	1,690	1,390	71.3	79.4	57.2	8.62							
II	23	1,690	86.6	91.4	53.6	12.9	1,570	70.0	79.8	62.5	9.28	1.21	0.87	4.9	6.5	1.03	1.6	
	24	1,690					1,280	63.8	70.4	62.7	9.00							
	25	1,690					1,510	85.2	92.0	57.1	8.88							
	26	1,690					1,630	80.7	86.4	55.3	8.85							
III Com- pound E	27	1,690	86.4	93.4	53.5	12.9	1,300	59.0	61.8	57.6	8.02	4.80	0.98	6.9	21.2	2.11	2.9	
	28	1,690					1,420	69.3	76.6	70.0	9.28							
	29	1,690					1,490	73.3	81.3	60.2	9.33							
	30	1,690					1,460	99.6	107.3	62.0	10.18							
IV Com- pound E	31	1,690	83.1	90.5	50.6	12.5	1,240	73.2	77.4	56.3	10.52	2.15	0.81	5.0	14.2	1.21	2.9	
	32	1,690					1,430	81.4	67.2	63.2	12.06							
	33	1,690					1,160	65.4	67.2	57.1	12.32							
	34	1,690					1,370	77.9	95.3	41.8	11.60							
V	35	1,690	84.3	91.2	57.7	13.2	1,860	77.2	79.3	46.1	12.18	1.09	1.08	6.8	16.0	1.48	3.5	
	36	1,690					970	53.8	57.3	42.3	11.08							
	37	1,690					1,360	64.0	70.7	51.0	10.80							
	38	1,690					1,530	86.2	87.0	48.5	8.94							
VI	39	1,690	850	32.7	37.7	61.7	8.59	0.92	1.08	6.5	13.7	1.40	3.8	
	40	1,690	1,500	68.7	73.5	62.2	9.01							
	41	1,690	1,040	48.4	57.2	63.5	8.72							
	42	1,690	1,040	51.9	61.3	62.7	8.60							

four-hour urinary excretion of reducing substances was determined by Benedict's method.

Results. The results are shown in Figure 4 and Table iv. No subjective change was noted. Compound E (80 mg. daily) appeared to have minimal effects on water and salt metabolism. There was no increase in weight or significant change in urine volume but a transient decrease in urinary sodium and chloride as well as evidence of hemo-

ment began. Serum sodium concentration fell slightly together with reciprocal changes in serum potassium. Compound E administration was associated with a decrease in serum phosphorus concentration, a very slight decline in total cholesterol and possibly a small increase in 17-ketosteroid and "corticoi-d" excretion. The total stool fat was not modified significantly. Fasting blood sugar levels were higher during the period of steroid treatment. On the fourth day after

the start of Compound E the peak levels of blood sugar were higher than in other glucose tolerance tests, and the character of the curve was more abnormal on both tests conducted during the treatment pe-

show considerable fluctuation. Nevertheless, there was a suggestive increase in some readings during Compound E administration, followed by a decrease in average values after the drug was discontinued.

TABLE IV(b)

Period	Hospital Day	Weight	"Rest-ing" B.P.	Sed. Rate	Hemato-erit	W.B.C.	Neutro-phil	Lympho-cytes	Eosino-phil	Blood Sugar and Glucose Tolerance					
		Kg.	Mm. Hg	mm./hr.	% Cells	Cells/cu. mm.				Fast-ing	½ hr.	1	2	3	4
										Mg./100 cc.					
I	19	72.90	178/86	30	44.5										
	20	72.81													
	21	73.00	176/90												
	22	72.86	158/78	5,000	3,125	1,750	44	116	...	270	198		
II	23	72.83	162/82	..	42.2										
	24	72.69	154/76	7,680	4,631	2,803	61	144	334	250			
	25	72.84	156/78												
	26	72.54	154/74	8,080	5,271	2,464	45	108	303	256	213	171	125
III Com- pound E	27	72.54	168/90	..	42.8	9,530	6,757	2,287	22						
	28	72.38	152/76												
	29	72.40	168/80												
	30	72.28	164/70	167	334	308	241	172	152
IV Com- pound E	31	71.87	194/94	..	38.9										
	32	71.91	156/80	9,150	6,771	2,104	28						
	33	71.69	150/70												
	34	71.95	180/88	11,480	8,830	2,411	57	167	278	242	228	222	189
V	35	71.65	144/72	35	39.8										
	36	71.36	158/78												
	37	71.79	126/60												
	38	71.64	170/78	8,290	5,389	2,518	156	137	294	227	184	163	127
VI	39	71.34	126/68	..	37.8	8,500	5,270	2,975	120						
	40	71.79	144/72												
	41	71.60	130/66												
	42	71.65	144/72												
	43	71.75	146/74												

riods. The total daily excretion of reducing substances was markedly increased in association with the drug administration. Daily urine samples throughout the experiment were negative for acetone and diacetic acid.

The sedimentation rate remained unaltered and teleroentgenograms and serial electrocardiograms were not modified.

Despite the usual baseline period, "rest-ing" blood pressure values continued to

COMMENT

It must be emphasized that the results obtained in this study represent short-term observations on a limited number of patients treated with 11-dehydro-17-hydroxy-corticosterone acetate.* It is not known whether Compound E, either free or esterified, con-

*Furnished through the courtesy of Merck and Co., Inc., Rahway, N. J., in the form of a suspension in peanut oil, each cc. containing 10 mg.

stitutes a hormone normally elaborated by the adrenal cortex. Furthermore, it is not known whether 80 mg. per day represents a small or a large dose, particularly since only a minute fraction of this dose appears in the urine as a "corticoid" as compared with the large amounts of "corticoid" material presumably elaborated by the adrenal cortex; moreover, there is the possibility of suppression of the patients' own adrenal cortical function by this steroid.

In all patients tested Compound E produced slight to moderate salt and water retention, usually with evidence of hemodilution. This was followed by a conspicuous diuresis in one subject. In the Addisonian patient on the first day of drug treatment this retention was preceded by a transitory increase in the excretion of water, sodium and chloride. In contrast to the familiar electrolyte effects of desoxycorticosterone acetate, the use of Compound E was associated with a small decline in serum sodium concentration of from 1.8 to 3.2 mEq. during the period of steroid administration.

With the dosage of Compound E employed no major changes in the excretion of potassium were evident. However, mention should be made of another patient with uncomplicated hypertensive vascular disease who received a daily dose of 150 mg. on two separate occasions. Although detailed studies were not undertaken, a transitory increase in potassium excretion of about 40 mEq. was noted during the first twenty-four hours, preceding the usual but transient retention of water or sodium. This phenomenon also occurred in the same patient upon the administration of adrenocorticotrophic hormone.

A negative nitrogen balance was observed in two patients, appearing only after a few days of Compound E treatment. A significant change was not apparent in the subject with Addison's disease. Despite the modification of carbohydrate metabolism the increased nitrogen excretion was not considered proof of increased conversion of protein to carbohydrate, although such a mechanism may be responsible.

In three of the four patients small in-

creases in fasting blood sugar and slight alterations in glucose tolerance curves were obtained during the course of Compound E therapy. The increase in twenty-four-hour excretion of reducing substances in the diabetic subject indicated that these changes were real. The fourth patient, a hypertensive treated for five days, showed no change in fasting blood sugar values. No glycosuria developed in the non-diabetic patients but traces of acetone appeared in two instances, limited to the fourth day of steroid administration. Although the excretion of reducing substances by the diabetic rose sharply, it must be recalled that small increases in blood sugar above renal threshold values would be sufficient to account for this degree of glycosuria and that the possible contribution of a change in threshold has not been investigated. In the non-diabetic patients the alterations in carbohydrate metabolism produced by Compound E were of small magnitude. In the one Addisonian patient studied the effect on the seventeen-hour fasting blood sugars and glucose tolerance curves would not justify the conclusion that this agent will prevent or modify the hypoglycemia with complete regularity in hypoadrenalism.

The rise in total white blood cell count and the fall in eosinophiles observed in three patients including the one with Addison's disease implies that Compound E may act directly on leukocytic mechanisms.

Small changes in "resting" blood pressure were apparent in all patients. These, however, were consistently greater than those observed in this clinic in control hypertensives treated with placebos and for similar periods of time. Whereas the arterial tension declined during or after therapy in the hypertensive subjects, it rose in the patient with adrenal cortical insufficiency more than would be expected on the basis of salt and water retention alone. It should be recalled that desoxycorticosterone acetate, which provokes comparable degrees of salt and water retention (but no reduction in serum sodium concentration), has been found to exhibit pressor properties when studied under similar conditions in hyper-

tensive patients.¹⁸ The difference in response of the Addisonian patient and the delayed effect on "resting" blood pressure in all subjects imply that Compound E has no direct humoral action. These observations supplement the results obtained with an adrenal cortical extract¹¹ and suggest that the drop in blood pressure produced by the extract may have been due to Compound E-like substances. If the rise in arterial tension observed in the patient with Addison's disease was not attributable to an increased blood volume, it is possible that this steroid requires the presence of an intact adrenal for its depressor effect and may act as a pressor agent in the absence of the adrenals.

CONCLUSIONS

1. Clinical and metabolic studies were undertaken in two patients with hypertensive vascular disease, one with Addison's disease, and one with hypertension and diabetes in order to determine the effects of 11-dehydro-17-hydroxy-corticosterone acetate (Compound E) administration in doses of 80 mg. daily.

2. Compound E induced small to moderate retention of salt and water, slight reductions in serum sodium concentration, inconstant negative nitrogen balance, small changes in carbohydrate metabolism (and, in two patients, transient acetoneuria) and a drop in total cholesterol not at the expense of the free cholesterol.

3. An increase in circulating white blood cells, due primarily to polymorphonuclear leukocytes, together with a drop in eosinophiles, was recorded in three patients including the one with hypoadrenalism.

4. Compound E exerted a depressor effect on the "resting" blood pressure of the hypertensive patients and a rise in pressure in the Addisonian patient.

Acknowledgments: We are indebted to Miss Ann D. Barrows, dietitian, and to Miss Margaret G. Hawthorne, head nurse, for their invaluable assistance.

REFERENCES

1. MASON, H. L., MYERS, C. S. and KENDALL, E. C. The chemistry of crystalline substances isolated

- from the suprarenal gland. *J. Biol. Chem.*, 114: 613-631, 1936.
2. WELLS, B. B. and KENDALL, E. C. The influence of corticosterone and C₁₇ hydroxydehydrocorticosterone (Compound E) on somatic growth. *Proc. Staff Meet., Mayo Clin.*, 15: 324-328, 1940.
3. WELLS, B. B. and KENDALL, E. C. The influence of the adrenal cortex in phlorizin diabetes. *Proc. Staff Meet., Mayo Clin.*, 15: 565-573, 1940.
4. INGLE, D. J. and THORN, G. W. A comparison of the effects of 11-desoxycorticosterone acetate and 17-hydroxy-11-dehydrocorticosterone in partially depancreatized rats. *Am. J. Physiol.*, 132: 670-678, 1941.
5. INGLE, D. J. The production of glycosuria in the normal rat by means of 17-hydroxy-11-dehydrocorticosterone. *Endocrinology*, 29: 649-652, 1941.
6. THORN, G. W., ENGEL, L. L. and LEWIS, R. A. The effect of 17-hydroxycorticosterone and related adrenal cortical steroids on sodium and chloride excretion. *Science*, 94: 348-349, 1941.
7. LONG, C. N. H. A discussion of the mechanism of action of adrenal cortical hormones on carbohydrate and protein metabolism. *Endocrinology*, 30: 870-883, 1942.
8. KUIZENGA, M. H., NELSON, J. W. and INGLE, D. J. The effect of 17-hydroxy-11-dehydrocorticosterone on the growth of young adrenalectomized rats. *Am. J. Physiol.*, 139: 499-503, 1943.
9. THORN, G. W., KOEFF, G. F., LEWIS, R. A. and OLSEN, E. F. Carbohydrate metabolism in Addison's disease. *J. Clin. Investigation*, 19: 813-832, 1940.
10. THORN, G. W. and CLINTON, M., JR. Metabolic changes in a patient with Addison's disease following the onset of diabetes mellitus. *J. Clin. Endocrinol.*, 3: 335-344, 1943.
11. PINES, K. L., PERERA, G. A., VISLOCKY, K. and BARROWS, A. N. Effect of adrenal cortical extract in hypertensive subjects. *Proc. Soc. Exper. Biol. & Med.*, 68: 286-288, 1948.
12. GOLDENBERG, M., SNYDER, C. H. and ARANOW, H., JR. New test for hypertension due to circulating epinephrine. *J. A. M. A.*, 135: 971-976, 1947.
13. CALLOW, N. H., CALLOW, R. K. and EMMENS, C. W. Colorimetric determination of substances containing the grouping $-\text{CH}_2\text{CO}-$ in urine extracts as an indication of androgen content. *Biochem. J.*, 32: 1312-1331, 1938.
14. DAUGHADAY, W. H., JAFFE, H. and WILLIAMS, R. H. Chemical assay for "cortin"; determination of formaldehyde liberated on oxidation with periodic acid. *J. Clin. Endocrinol.*, 8: 166-174, 1948.
15. THORN, G. W., FORSHAM, P. H., PRUNTY, F. T. G. and HILLS, A. G. A test for adrenal cortical insufficiency; the response to pituitary adrenocorticotrophic hormone. *J. A. M. A.*, 137: 1005-1009, 1948.
16. PETERS, J. P. and VAN SLYKE, D. D. Quantitative Clinical Chemistry. Vol. 2, p. 492. Baltimore, 1932. Williams and Wilkins Co.
17. WERNER, S. C., QUIMBY, E. H. and SCHMIDT, C. The clinical use of radioactive iodine. *Bull. New York Acad. Med.*, 24: 549-560, 1948.
18. PERERA, G. A. and BLOOD, D. W. Pressor activity of desoxycorticosterone acetate in normotensive and hypertensive subjects. *Ann. Int. Med.*, 27: 401-404, 1947.

Role of the Neurohypophysis in the Pathogenesis of Hypertension and Some Allied Disorders Associated with Aging*

THOMAS FINDLEY, M.D.

New Orleans, Louisiana

THE frequency with which aging is accompanied by such disturbances as hypertension, arteriosclerosis, obesity, diabetes mellitus and sexual impotence suggests that these disturbances may reflect the gradual failure of some as yet unknown homeostatic mechanism. This paper assembles the evidence which supports the view that hypofunction of the neurohypophysis may represent a common pathogenetic denominator. It is written in full awareness that the theory to be set forth is far from proved but also in appreciation of the value of Charles Darwin's statement that "without hypothesis there can be no useful observation."

The present concept was first presented by Heinbecker¹⁻⁴ but his experiments and deductions are not as widely appreciated as they should be. We here present additional data from the literature which appears to be relevant.

CUSHING'S SYNDROME

A discussion of Cushing's syndrome affords a suitable point of departure. It is possible to accept the view that a patient with this disorder may simply be an unfortunate person in whom, for reasons to be discussed later, many of the ills which beset aging man are concentrated in unhappy intensity. This broad biologic viewpoint seems justified when one considers the chief manifestations separately. The classic fea-

tures are, of course, obesity, hypertension, arteriosclerosis, an insulin-resistant type of hyperglycemia, sexual impotence, osteoporosis, muscular weakness and frequently cancer. There are often other abnormalities as well but these seem to be the most important, and it is obvious that they are the very disorders which contribute so heavily to the morbidity and mortality of later life. It taxes credulity to assume that when all these disturbances are assembled in one person said then to have Cushing's syndrome, each of them has developed by a special mechanism not operating in individuals less spectacularly afflicted. There is no proof that any one of these features of Cushing's syndrome differs fundamentally from the same feature appearing much more commonly in the general population. It is tempting to conclude that when Cushing's syndrome is understood the most commonly and deadly afflictions of old age will also be understood and that in many persons there develops with increasing maturity one or more facets of this complex disorder which is so dramatic in its full-blown form.

The bodies of many persons with Cushing's syndrome contain tumors of one endocrine gland or another—the adrenal cortex most commonly—but also the anterior pituitary, thymus or ovary on occasion. Of those without tumor many have unmistakable hyperplasia of both adrenal

*From the Departments of Medicine, Tulane University of Louisiana, School of Medicine and the Ochsner Clinic, New Orleans, La.

cortices. Still others have shown no gross abnormality whatever of any endocrine gland.⁵ The only common denominator thus far demonstrated which links all these cases together is the peculiar hyalinization of the basophilic cells in the anterior pituitary described by Crooke⁶ and accepted by others.⁷⁻⁹ Although opinion¹⁰ is not unanimous concerning the specificity of these cellular changes, it appears to be nearly so, and it is therefore mandatory that the origin and significance of these Crooke cells be explained since they seem to represent the key to the problem.

The only clue yet to appear comes from the study of that especially intriguing group of cases with no evidence of endocrine tumor or adrenocortical hyperplasia, and here again another apparent common denominator has recently been described. Influenced by previous studies on dogs which showed that destruction of certain hypothalamic nuclei causes obesity and other changes reminiscent of Cushing's syndrome,¹¹ Heinbecker¹ reported that four such patients showed atrophy of the paraventricular nuclei in association with Crooke cells; a fifth patient with cancer of the adrenal cortex had Crooke cells but normal hypothalamic nuclei. The idea was then propounded that the integrity of the basophiles and their respective end organs is dependent upon hormones issuing from the neurohypophysis, and that depression of basophilic function results in relative hyperfunction of the pituitary eosinophiles and their respective end organs. Basophilic hypo-activity can be induced either by any neurologic event which inhibits the function of the neurohypophysis or, more commonly perhaps, by the formation in excessive amounts of other hormones physiologically antagonistic to those of the neurohypophysis. The basic observation concerning the effect of hypothalamic lesions upon the structure and function of the anterior pituitary has not yet been confirmed but an attempt will be made here to see if available collateral evidence can be interpreted in favor of this doctrine.

EFFECTS OF HYPOTHALAMIC LESIONS

Information concerning the effects of hypothalamic lesions upon homeostasis is meager, but enough is available to justify the suspicion that the neurohypophysis may be an important regulator of the processes under discussion.

Obesity. Without questioning in the least the demonstration by Newburgh¹² and Conn¹³ that the same thermodynamic relations exist in obese as in normal persons, it seems possible to suggest that qualitative metabolic differences may exist within a normal quantitative frame. No one questions the fact that the obesity in Cushing's syndrome associated with adrenocortical tumor or hyperplasia is promoted by hormones emanating from that gland; indeed Albright¹⁴ has postulated that the fundamental defect in these forms of Cushing's syndrome is the overproduction of adrenocortical hormones which promote the formation of glucose from protein and suppress the peripheral oxidation of glucose. The present theory suggests that a state of relative hyperadrenocorticism exists when basophilic function is depressed and eosinophilic function is therefore unopposed. Or, conversely, it may be said that hypofunction of the neurohypophysis and its dependent basophiles may sensitize the organism to adrenocortical hormones in such a way as to promote the storage of fat.

The development of obesity in animals with hypothalamic lesions has recently been reviewed by Brobeck.¹⁵ The most effective lesions involve the ventromedial nuclei and they cause gain in weight chiefly by increasing appetite and diminishing physical activity. Striking gain or loss of weight is commonly seen clinically in association with lesions in this area of the brain. It appears that concomitant injury to the anterior pituitary is not a factor.¹⁶

Histologic observations in simple obesity are scarce but there are some which suggest the co-existence of basophilic degeneration. Ranson and associates¹⁷ produced adiposity and diabetes mellitus in a monkey with

bilateral hypothalamic lesions and Rasmussen¹⁸ noted basophilia in its anterior pituitary. In a review of the literature Goldzieher¹⁹ found that basophilia was a common but not constant anatomic change; he also reported ten cases of obesity with increased numbers of basophiles and chromophobes and nine control patients without such disproportions. Heinbecker⁴ has produced basophilic degeneration by denervation of the neurohypophysis and increased the number of basophiles by administering pitressin. Failure to demonstrate histologic abnormalities in the hypothalamus and pituitary²⁰ does not, of course, preclude the possibility of functional depression of neurohypophyseal activity or of hormonal counterbalance in peripheral tissue.

There is also evidence, equivocal and unconvincing as it may be at the present, that pituitrin itself modifies fat metabolism. Several studies have shown the capacity of this hormone to produce fatty infiltration of the liver, presumably by transferring fat from other depots²¹⁻²⁵ although the existence of a separate hormone "liputrin"²⁵ has not been confirmed. Van Dyke²⁶ stated that extracts of the posterior pituitary probably do not significantly affect the concentration of cholesterol and phosphatides in the blood of normal mammals. Blotner²⁷ observed this to be true in normal humans but claimed that pituitrin abolishes alimentary hyperlipemia in patients with obesity or diabetes insipidus.

In view of the constancy with which most young people maintain their body weight in absolute conscious disregard of caloric intake or energy output and the almost universal tendency of older people to become heavier, it seems reasonable to suppose that obesity is not always a matter of gluttony or sloth. It is here suggested that subtle changes in the metabolic mixture occur as age produces diminished secretions of adrenocortical antagonists.

Diabetes Mellitus. The capacity of the eosinophile-adrenocortical complex to induce an insulin-resistant type of hyperglycemia is demonstrated clinically by its

frequent occurrence in acromegaly and in Cushing's syndrome, and experimentally by Heinbecker and Rolf's²⁸ demonstrations that insulin sensitivity is greatly increased when eosinophilic function is impaired. Heinbecker² has furthermore shown that denervation of the neurohypophysis increases the resistance of dogs to the effects of insulin. Histologic evidence of eosinophilic proliferation in human diabetes mellitus has been both denied²⁹ and reported.³⁰⁻³¹ The amelioration of pancreatic diabetes by hypophysectomy or adrenalectomy is, of course, well known as is the insulin-sensitivity of patients with Simmonds' disease.

Destructive lesions in the hypothalamus are known to modify carbohydrate metabolism but the results are difficult to interpret because of possible concomitant injury to the anterior lobe and because the nerve supply to the liver, adrenals and pancreas may also be disturbed. Chronic hyperglycemia has, however, occasionally been produced in animals by lesions involving the lateral nuclei^{17,33,34} and Morgan and associates³⁵ described atrophy of the paraventricular nuclei in each of fifteen cases of clinical diabetes mellitus. Carbohydrate tolerance diminishes with age.³⁶

The hyperglycemic action of pituitrin is apparently inconsistent with this general thesis but the mechanism of this action is not at all understood.³⁷ It must be admitted that no reports have been found which suggest that neurohypophyseal extracts have an insulin-like action.

Diabetes Insipidus. Of all the hypothalamic functions that of control of water metabolism is perhaps the best understood. There appears to be almost universal agreement that the integrity of the supra-opticohypophyseal tract is necessary if enough antidiuretic hormone is to be elaborated by the neurohypophysis to permit the renal tubules to absorb proper amounts of glomerular filtrate.^{38,39} Destruction of this same tract is not the only important factor, however, for the control of water balance also depends upon the

action of the adrenal cortex.^{40,41} Adrenalectomy greatly reduces the fluid exchange in cats with diabetes insipidus and pitressin prolongs the lives of adrenalectomized cats with diabetes insipidus.⁴² The prolonged water diuresis of humans with diabetes insipidus⁴³ resembles that seen in adrenal insufficiency.⁴⁴ Gersh and Grollman⁴⁵ noted no anatomic changes in the neurohypophyses of rats dead of adrenal insufficiency but Martin and associates⁴⁶ claimed that hyperfunction of the posterior pituitary follows adrenalectomy. From a clinical point of view the combination of hypopitressinemia and relative hyperadrenocorticism might well explain the low grade polyuria of elderly persons who have no abnormalities of the lower urinary tract, as well as that so often seen in diabetes mellitus, obesity and Cushing's syndrome.

Gonadal Failure. The association between hypothalamic lesions and hypogonadism, long recognized clinically, has recently been reviewed by Bard.⁴⁷ Dey⁴⁸ reported that genital atrophy is caused by lesions involving the median eminence whereas injury to the anterior hypothalamus produces genital hypertrophy and pronounced ovarian follicular development due to lack of luteinizing hormones. Brooks⁴⁹ believed that there are enough nerve pathways between the hypothalamus and the anterior pituitary to justify the assumption that the output of gonadotrophic hormone is at least in part regulated by the central nervous system, a viewpoint strengthened by the demonstration⁵⁰ that section of the pituitary stalk has a definite effect upon the estrous cycle of guinea pigs. Heinbecker¹ attributed gonadal failure to loss of basophilic function. By comparing the changes in dogs produced by denervation of the neurohypophysis with those following total hypophysectomy (the median eminence is also destroyed), he found that the basophiles are trophic to the thyroid, the follicular cells of the ovary and the sperm cells of the male. Confirmation of these observations might then explain the frequent association of gonadal failure with obesity, diabetes mellitus,

"menopausal hypertension" and Cushing's syndrome. It might also account for the relatively high incidence of hypometabolism and hypercholesterolemia in these conditions. Gonadal failure is often associated with experimental⁵¹ and clinical⁵² diabetes mellitus.

Osteoporosis. Albright⁵³ has recently reviewed his studies which show that some forms of osteoporosis are associated with disturbances in the metabolism of protein rather than with defects in the ability of the body to handle minerals. In Cushing's syndrome and other diseases of adaptation osteoporosis is attributed to excess of these adrenocortical hormones which accelerate gluconeogenesis; in old age loss of gonadal hormones and excess of adrenocortical "N-hormone" appear to be important. Regardless of the precise mechanism, hyperadrenocorticism—absolute or relative—is obviously a fundamental contributing factor in the common types of skeletal demineralization.

Blood Pressure. It remains to inquire whether a similar approach may not clarify the pathogenesis of chronic diastolic hypertension. A satisfactory theory concerning the pathogenesis of hypertension must take into account the following factors: (1) Genetic variations which make one person's blood vessels more susceptible than another's to stimulation and disease; (2) psychogenic influences which result in personality disorders; (3) lack of evidence for increased sympathetic tone in at least the majority of patients with essential hypertension; (4) the remarkable similarity between experimental renal and clinical essential hypertension; (5) the tendency of "renal" hypertension to assume a chronic "non-renal" form; (6) the probable causal relationship between hyperadrenocorticism and the diseases of adaptation; (7) frequent association of high blood pressure with old age, arteriosclerosis, obesity, hyperglycemia, hypercholesterolemia, sexual impotence, polyuria, osteoporosis, pregnancy, renal diseases and benign prostatic hypertrophy.

To date, the chief obstacle to acceptance

of the humoral origin of hypertension is the consistent failure of many workers to demonstrate increased amounts of pressor materials in biologic fluids of animals and humans with chronic hypertension.⁵⁴ Negative hormone assays, however, do not exclude the possibility that the organism has become sensitized to normal amounts of circulating pressor substances, and the essence of the present theory is that appropriate lesions in the hypothalamus create this condition of relative pressor excess by diminishing the production of antipressor substance. More specifically, it is postulated that destruction of the paraventricular and supra-optic nuclei and the consequent depression of neurohypophyseal activity so alters the eosinophile-basophile activity ratio of the anterior lobe as to create a state of heightened tissue responsiveness to the combined actions of such pressor materials as desoxycorticosterone, progesterone, renin and epinephrine. If this is true, then the fact that essential hypertension is often not accompanied by demonstrable overproduction of specific steroids,⁵⁵⁻⁵⁷ renin⁵⁸ and epinephrine,⁵⁹ loses force. There is at the present time much suspicion but no proof that dysfunction of the adrenal cortex exists in essential hypertension. Gross pathologic observations have been of little value. Claims have been made that hyperplastic and adenomatous changes in the adrenal cortex occur with significant frequency in hypertension and diabetes mellitus⁶⁰⁻⁶⁴ although the evidence to the contrary seems more convincing.^{56, 65-67} Histologic studies have been equally inconclusive although a systematic application of the Ponceau fuchsin reaction is obviously needed.⁶⁸ The physiologic approach has been somewhat more productive, particularly the demonstration by Selye^{70, 71} and others⁷² that certain steroid hormones can under certain conditions cause hypertension and various vascular lesions. Obliteration of experimental renal hypertension by adrenalectomy and its re-appearance following substitution therapy has been amply confirmed;^{73, 74} Selye⁵⁷ reported that some patients with es-

sential hypertension exhibit the high serum $\frac{\text{Na}}{\text{Cl}}$ ratio reminiscent of Cushing's syndrome. Knowlton and co-workers⁷⁵ showed that hypersensitivity to desoxycorticosterone acetate and sodium also exists in rats with serum-induced nephritis. Perera⁷⁶ reported the case of a man with established hypertension whose blood pressure dropped with the onset of Addison's disease and increased under the influence of desoxycorticosterone acetate; he⁷⁷ showed that hypertensive humans withstand salt deprivation much more easily than normal subjects do and that sodium potentiates the pressor activity of desoxycorticosterone acetate in hypertensive subjects,⁷⁸ and, importantly from the standpoint of the present thesis, he⁷⁹ claimed that patients with essential hypertension are hypersensitive to the pressor action of desoxycorticosterone acetate. In later papers, however, he^{79a and 79b} reported that this response gradually disappears despite continued administration of this steroid and that desoxycorticosterone glucoside and adrenal cortical extract have no pressor activity in hypertensive humans. Goldman and Schroeder^{79c} also reported that hypertensive humans are abnormally sensitive to the blood pressure-raising action of DOCA but that propylene glycol, adrenal cortical extract, progesterone, testosterone, dehydroisoandrosterone acetate, Δ^5 pregnenolone and 17-hydroxy-11-dehydrocorticosterone had no such pressor activity when given intravenously. An obvious contrast can, of course, be made between the hypertension of Cushing's syndrome and the hypotension of Addison's disease, and the present interest in sodium depletion as a method of treating high blood pressure testifies to the probable alterations in adrenocortical function.⁸⁰

Any experimental method which will induce eosinophilia of the anterior pituitary, therefore, assumes prime importance for these cells appear to be trophic to the adrenal cortex. The validity of this concept and its associated implications rests solely upon the unconfirmed experiences of Heinbecker¹⁻⁴ with three different types of

neurosurgical procedures illustrated diagrammatically in Figure 1. Simple hypophysectomy (A) is functionally equivalent to anterior lobectomy since the median eminence and part of the stalk remain as sources of neurohypophyseal hormone. Total

hypophysectomy (operation B) leads to the further conclusion that the eosinophils, on the other hand, are trophic to the heart, renal tubules, adrenal cortex, corpus luteum, the cells of Leydig and the prostate. These organs do not atrophy following denerva-

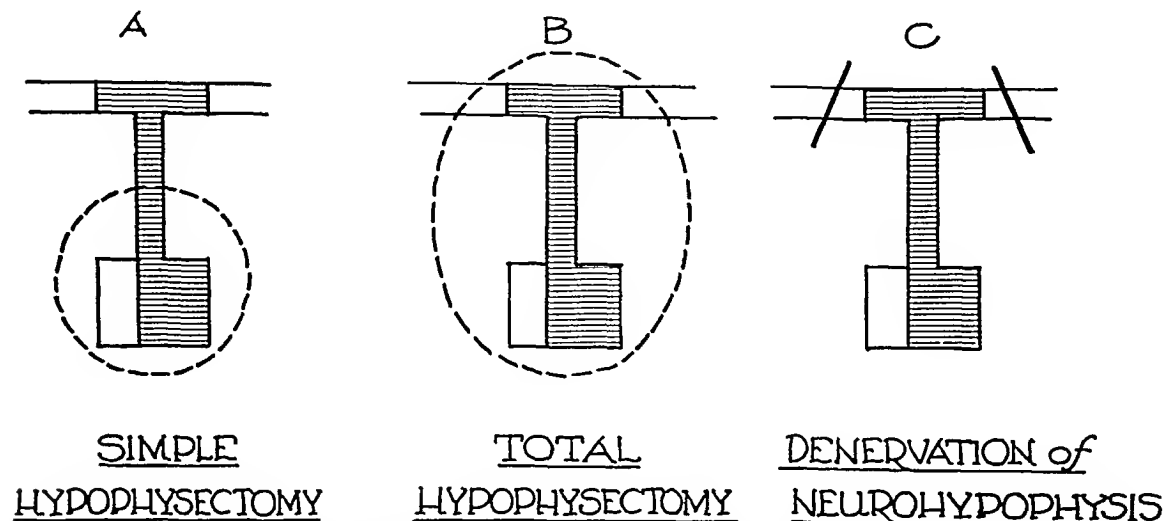


FIG. 1. Heinbecker's technic for separating the eosinophilic and basophilic functions of the anterior pituitary. Operation C produces only basophilic degeneration.

hypophysectomy (B) represents excision of all anterior and posterior lobe tissue. Denervation of the neurohypophysis by appropriate incisions in the anterior and posterior hypothalamus (C) is functionally equivalent to neurohypophysectomy since all pituitrin-forming tissue is inactivated without concomitant damage to the anterior lobe. Heinbecker's fundamental contribution consists of his demonstration that in dogs operation C is followed, after a latent period of a few months, by profound histologic and physiologic changes in the anterior pituitary. Such preparations⁴ show not only a large reduction in the number of basophiles but also degenerative changes in the few which remain; the anterior lobe consists almost entirely of eosinophiles and chromophobes with only a sprinkling of degranulated turbid basophilic elements. Since these animals also show regressive changes in the thyroid, follicular cells in the ovary and the sperm cells in the male, it is furthermore assumed that hormones from the basophiles are trophic to these glands. Comparison of these observations at autopsy with those in animals totally

tion of the neurohypophysis with its attendant basophilic degeneration nor does this operation modify the hypertrophy of the remaining kidney or adrenal in such animals which are also unilaterally nephrectomized or unilaterally adrenalectomized. The importance of the pituitary eosinophiles in the regulation of the circulation is shown by the extremely high urea clearance in acromegaly⁸¹ and by the profound reduction in arterial pressure, cardiac output, renal blood flow and diodrast-Tm which follows simple or total hypophysectomy but not denervation of the neurohypophysis.^{3,82,83} Growth may be largely a function of blood flow.

Confirmation of these claims is urgently needed for they possess startling implications. Some of these are: (1) a correlation between cellular structure and function in the anterior pituitary exists which is not now generally conceded; (2) the growth and integrity of the basophiles depend upon humoral agents elaborated by the neurohypophysis; (3) hypofunction of the neurohypophysis sensitizes the organism to adrenocortical hormones and possibly to other

pressor substances as well and (4) the eosinophiles exert a profound effect upon the circulation.

Figure 2 shows schematically how hypothalamic lesions may produce basophilic degeneration with its attendant suppression

not been specifically repeated, supportive evidence is available from other sources. Mellgren's⁶⁸ quantitative studies of the cellular changes in the anterior pituitary and adrenal cortex in Cushing's syndrome and allied diseases are in accord although

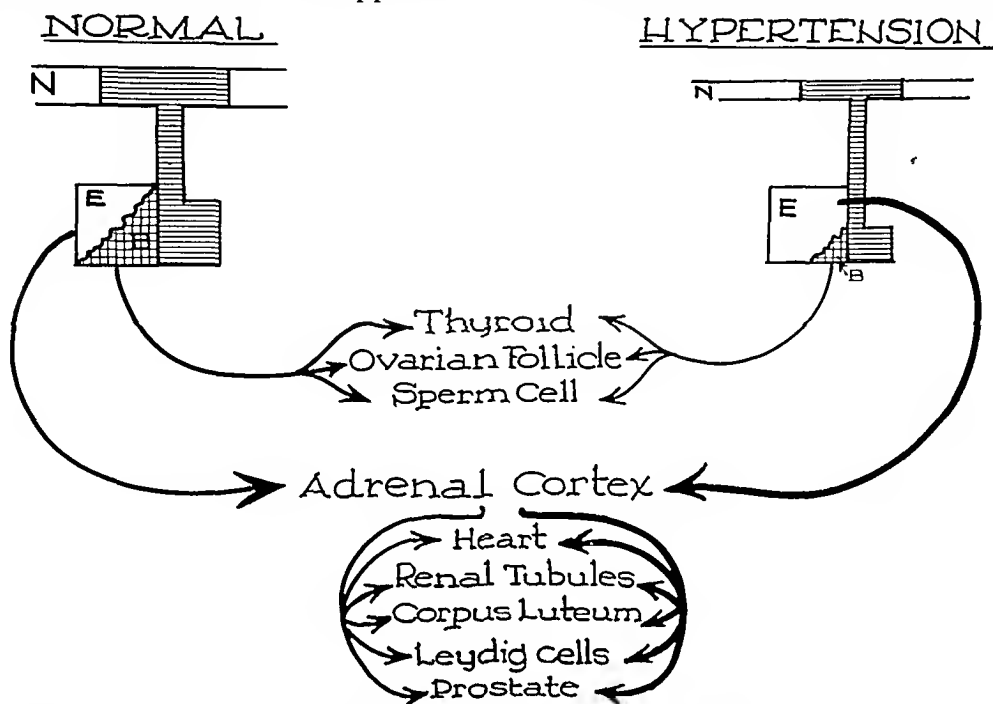


FIG. 2. Heinbecker's concept of the manner by which hypofunction of the neurohypophysis and degeneration of the anterior lobe basophiles result in relative hyperadrenocorticism.

of thyroid and gonadal function on the one hand and eosinophilic dominance with subsequent hyperactivity of the adrenal cortex and its various target organs on the other hand. If valid, the concept means that Cushing's syndrome, of which hypertension is a fundamental feature, can be produced by:

1. *Overproduction of Steroid Hormones.* This obviously accounts for the hypertension in those cases of Cushing's syndrome caused by tumor or hyperplasia of the adrenal cortex. For some unknown reason adrenocortical hyperplasia apparently also accompanies arrhenoblastoma⁸⁴ and cancer of the thymus.^{85,86} In these cases no hypothalamic lesion need be postulated; the Croke changes are due to neutralization of neurohypophyseal hormone by excessive corticoid.

2. *Destructive Lesions in the Hypothalamus.* Although Heinbecker's experiments have

his interpretations are at variance with those here offered. Without comment on the mechanism of the results obtained by Sevringhaus and Thompson,⁸⁷ it may be noted that they produced in a different manner the same combination of Croke cells and atrophy of the thyroid and gonads. Chronic hydrocephalus might be expected to initiate such a mechanism; Heinbecker¹ reported dramatic reversal of Cushing's syndrome in one case following removal of a meningioma from the foramen magnum, and Kraus⁸⁸ reported basophilic degeneration and adrenocortical hypertrophy in a series of patients with lesions in the region of the third ventricle. Rasmussen⁷ observed a rough correlation between basophilia and the age of the patient, a hint that nuclear abiotrophy might be the common denominator. Heinbecker¹ conversely reported that administration of

large amounts of pituitrin in normal dogs leads to basophilic proliferation. It is at least conceivable that increased intracranial pressure may occasionally be the cause of malignant hypertension rather than the result.

The fact that denervation of the neurohypophysis in dogs (operation c) did not result in severe and sustained hypertension¹ appears to offer a serious objection to the present theory, as is also the fact that no correlation between diabetes insipidus and hypertension has been described. In Heinbecker's³ series of patients with diabetes insipidus, however, a relatively high incidence of moderate hypertension was reported, and in our small series⁸⁹ of five patients three had blood pressures definitely higher than 140 diastolic and 90 systolic. It seems likely, however, that the paraventricular nuclei are more important than the supraoptic group from the standpoint of Cushing's syndrome; in addition to the evidence already cited, Sattler and Ingram⁹⁰ reported that section of the supra-opticohypophyseal tracts high in the median eminence of dogs with renal hypertension results in a decline of blood pressure, and DeBodo and Marine⁹¹ noted no endocrine abnormalities in dogs made polyuric by section of the same tract. Walter and Pijoan,⁹² on the other hand, produced severe and sustained hypertension in one dog by a small incision made transversely in the hypothalamus immediately posterior to the infundibulum.

3. *Functional Inhibition of the Neurohypophysis.* Perversion of function is not necessarily reflected in distortion of structure so that histologic evidence of eosinophile-adrenocortical dominance need not be demanded. Sustained cerebrocortical inhibition of hypothalamic nuclei in a person whose blood vessels are genetically predisposed to pressor stimuli must be a common combination. "Hypopituitrinemia"—a term to describe underproduction of neurohypophyseal hormones, known or unknown—may be of any grade and is probably seldom so complete as to raise

compensatory endocrine changes to the visual threshold. It usually requires half a lifetime for hypertension to develop. Afferent pathways to the hypothalamic nuclei are known to be widespread⁹³ but impulses from the frontal lobe are apt to be of special importance in the etiology of diseases of adaptation.

Arteriosclerosis. The experimental production of vascular lesions by adrenocortical substances⁷⁰ offers an important clue concerning the etiology of this common condition, and the deposition of cholesterol in atheromatous lesions suggests, of course, that disturbances in steroid metabolism are contributing factors.

Old Age. No studies concerning the effect of age upon the structure of the hypothalamus have been found, but Rasmussen⁷ observed increasing basophilia. The "adrenopause" comes later than the "menopause,"^{7,93} a fact which may have some bearing upon the acknowledged correlation of the disorders under discussion with increasing maturity or decay.

PITUITRIN ANTAGONISTS

If it be claimed that hypofunction of the neurohypophysis sensitizes the organism to pressor substances elaborated by the adrenal cortex, the kidney and other organs, it must be demonstrated that pituitrin is capable of neutralizing, at least in part, the action of certain known hormones.

Desoxycorticosterone Acetate (DOCA). It is not claimed that the effects of this hormone on salt and water metabolism are restricted to the neutralization of pitressin but, when given to normal animals in large amounts, DOCA produces a state of chronic polyuria similar in many ways to diabetes insipidus^{40,82,94} but differing from it in that it is relatively unresponsive to pitressin. Corey and Britton⁹⁵ observed that administration of DOCA to rats caused polydipsia, polyuria and reduced urinary excretory rates of sodium and chloride; the opposite effects were produced by pituitrin and when the two drugs were given together the action of pituitrin predominated. Zierler

and Lilienthal⁹⁶ produced in a man polyuria and polydipsia with DOCA. The ability of this substance to facilitate the re-absorption of sodium and water by the renal tubules is, of course, well known⁹⁷ and Shannon¹¹ attributes the capacity of dogs with diabetes insipidus to maintain blood volume during dehydration to maximal tubular re-absorption of sodium occasioned by pituitrin deficiency. The opposing effects of adrenocortical extract or DOCA and pitressin upon the renal excretion of minerals have also been emphasized by Anderson and Murlin⁹⁸ and McQuarrie and co-workers.⁹⁹ Winter and co-workers¹⁰⁰ showed that adrenalectomy in cats with diabetes insipidus is followed by the usual rise in serum potassium concentration but not by any consistent decrease in serum sodium or chloride. A complete review of this subject is beyond the scope of this paper but additional references¹⁰⁰⁻¹⁰³ are offered which suggest but do not prove the existence of neurohypophyseal-adrenocortical antagonism. Possible antagonistic effects of pituitrin upon other functions of the adrenal cortex seem not to have been studied in detail although it is reported⁴² that pitressin does not prolong the life of the adrenalectomized cat. However, the suggestion of Corey and Britton⁹⁵ that excess of pituitrin might cause a syndrome resembling adrenocortical insufficiency is quite in harmony with the Heinbecker hypothesis. Evidence that DOCA can cause sustained hypertension in normal animals¹⁰⁶⁻¹¹⁰ has not been universally confirmed.^{111,112}

Denervation of the neurohypophysis in dogs sensitizes the renal blood vessels to the constrictive action of DOCA.^{82,113} Perera and Blood⁷⁸ showed that humans with essential hypertension respond in an exaggerated manner to the pressor activity of DOCA given subcutaneously, and Goldman and Schroeder^{79c,114,115} have also observed this phenomenon following intravenous administration.

Progesterone. No specific studies concerning the effect of pituitrin on the actions of progesterone have been found but this

steroid is closely related chemically and physiologically to DOCA. It is known at least that the lives of adrenalectomized animals are prolonged by crystalline progesterone¹¹⁶ and by pregnancy.¹¹⁷ Reynolds and Allen¹¹⁸ reported that progesterone neutralizes the *in vitro* action of pituitrin on estrogen-primed uterine muscle. Goldman and Schroeder^{79c,114,115} have published conflicting claims concerning the acute pressor response of hypertensive humans to intravenously administered progesterone dissolved in propylene glycol. Progesterone induces hypertension in normal animals.^{108,110,119-121}

Renin. Antagonism between the posterior pituitary and the kidney may be suspected from the fact that administration of renin produces chronic polyuria¹²² and Oster and Martinez¹²³ reported polydipsia and polyuria in rats with renal hypertension. Frankel and Wakerlin,¹²⁴ however, observed that renal hypertension in dogs does not modify the output of antidiuretic substance in response to hydration and dehydration.

Heinbecker⁴ produced chronic hypertension and eosinophilia of the anterior pituitary in normal dogs by wrapping the kidneys in silk but when the same procedure was applied to animals whose neurohypophysis had been previously denervated, death rapidly ensued in a manner resembling that which Goldblatt¹²⁵ described after extreme constriction of the renal arteries. Animals with experimental renal hypertension are reported to be hypersensitive to renin¹²⁶⁻¹²⁸ but the data are not convincing. Pitressin is said to diminish the pressor action of angiotonin¹²⁹ but its effect upon renin has apparently not been reported. Failure of posterior hypophysectomy¹³⁰ or of section of supra-optico-hypophyseal tract⁹⁰ to intensify renal hypertension may have been due to incomplete removal or inactivation of neurohypophyseal tissue. The matter of hypersensitivity of hypertensive man to renin and angiotonin has not been reported.

Epinephrine. Increased sensitivity to epinephrine has been reported in hyper-

tensive animals¹³¹⁻¹³³ and man¹³⁴⁻¹³⁷ but these results should be interpreted with caution since hypertensive subjects often appear to hyper-react to a variety of stimuli. Epinephrine does, however, greatly intensify the vasoconstrictive properties of certain proteins derived from various tissues, including the kidney,¹³⁸ and it is a substance capable of stimulating the formation of adrenotrophic hormone.¹³⁹

COMMENTS

The present hypothesis has many attractive aspects. It assigns to the central nervous system the important role in the pathogenesis of hypertension and allied diseases which it deserves. Heretofore, the vasomotor centers have received consideration because of the great importance of the adrenergic system in the adjustment of the organism to emergency situations, but there is no convincing evidence that sympathetic tone is increased in chronic essential hypertension.^{140-142a} The shifting of emphasis from the medulla oblongata to the more ancient structures comprising the floor of the third ventricle opens a new approach to the study of the aging process, which should appeal to students of psychosomatic medicine who have long been aware of the disastrous effects which chronic friction between the personality and its environment may exert upon the cardiovascular system.¹⁴³⁻¹⁴⁵ One would like to find anatomic evidence of hypothalamic disease and basophilic degeneration in all cases of continued diastolic hypertension but Rasmussen⁷ was unable to do so. No structural changes may be anticipated, however, if one assumes that chronic hypopituitrinemia can be produced in constitutionally susceptible persons by sustained inhibition of the hypothalamus from impulses arising from centers higher in the brain.

This theory accounts for the fact that no chemical evidence of increased hormonal production is usually found as strong hints exist that neurohypophyseal extracts antagonize several important pressor hormones. Cerebral abiotrophy with dimin-

ished secretion of the only hormone the brain is known to produce seems to be a logical event in the aging process, and this deficiency brings with it a state of *relative* hyperadrenocorticism. Heinbecker⁴ even reported that denervation of the neurohypophysis produces lymphopenia, a consistent accompaniment of certain forms of adrenocortical hyperfunction. Eosinophilic dominance may also be produced by the action of large amounts of DOCA,² progesterone and renin^{4,146} although the "endocrine kidney" of Selye⁷¹ seems to secrete an antirenotrophic substance. Special types of hypertension, of course, are apt to appear in younger persons when overproduction of pituitrin-antagonists occurs with primary diseases of the adrenal cortex and kidney and in pregnancy, but the fundamental mechanism may be the same.

This hypothesis may explain the fact that hypertension of purely renal origin eventually becomes non-renal in nature,¹⁴⁷ the experimental observations being supported by clinical experience that nephrectomy seldom modifies the hypertension associated with unilateral renal disease unless the operation is done early. Significant amounts of renin have been observed in the blood of animals and man only in the early stages of hypertension or in acute disturbances of renal blood flow,^{148,149} so it appears that in established hypertension the need for excessive renin formation no longer exists. Heinbecker³ considers that renin production increases whenever the integrity of renal tubular tissue is threatened by disease or anoxia; the hypertension which it produces by constriction of extrarenal blood vessels is a compensatory phenomenon designed to maintain renal blood flow and glomerular filtration rate, and it is sustained by the neurohormonal mechanism herein described. If so, this compensatory effort performs its task at great expense to extrarenal organs and eventually destroys the kidney itself by producing vascular lesions. It is much too early to attempt a correlation between these views and those offered by Shorr and co-work-

crs^{150, 151} concerning the importance of vaso-active materials from the kidney and liver in the regulation of the circulation.

This theory accounts for the acknowledged frequency with which hypertension and arteriosclerosis are associated with obesity, hyperglycemia, hypercholesterolemia, gonadal failure, osteoporosis and polyuria. There is also reason to suspect that benign prostatic hypertrophy and hyperostosis frontalis interna are also variants of the same underlying disorder.⁶⁸

Finally, this theory suggests that preventive and therapeutic measures may be achieved through substitution therapy. Hypertension has been treated with pituitrin before¹⁵² but for precisely opposing reasons to those herein advocated. One should note that for every disorder known to be associated with hyperfunction of some phase of adrenocortical activity, an analogue seems to have been produced by destructive lesions involving the hypothalamus and its appendage. If this concept appears to violate the laws of endocrine homeostasis, it may be argued that the diseases under discussion are themselves expressions of disturbed homeostasis. In any event it offers a fertile field for further investigation.

SUMMARY

Evidence, derived largely from Heinbecker's experimental investigations, is assembled to support the view that hypertension and many allied disorders of aging are due to hypofunction of the neurohypophysis. Diminished secretion by this gland results in degeneration of the basophiles of the anterior pituitary and their respective target organs and in a state of increased tissue sensitivity to the combined action of various pressor hormones.

REFERENCES

- HEINBECKER, P. Pathogenesis of Cushing's syndrome. *Medicine*, 23: 225, 1944.
- HEINBECKER, P. Cushing's syndrome. *Ann. Surg.*, 124: 252, 1946.
- HEINBECKER, P. Factors limiting surgery for essential hypertension. *Ann. Surg.*, 126: 535, 1947.
- HEINBECKER, P. The pathogenesis of diastolic hypertension. *Surgery*, 23: 618, 1948.
- EISENHARDT, L. and THOMPSON, K. W. A brief consideration of the present status of so called pituitary basophilism; with a tabulation of verified cases. *Nale J. Biol. & Med.*, 11: 507, 1939.
- CROOKE, A. C. Change in basophil cells of pituitary gland; common condition which exhibits syndrome attributed to basophil adenoma. *J. Path. & Bact.*, 41: 339, 1935.
- RASMUSSEN, A. T. Relation of basophilic cells of human hypophysis to blood pressure. *Endocrinology*, 20: 673, 1936.
- THOMPSON, K. W. and EISENHARDT, L. Further consideration of Cushing syndrome. *J. Clin. Endocrinol.*, 3: 445, 1943.
- ANDERSON, E. and HAYMAKER, W. Cushing's syndrome. *J. Nerv. & Ment. Dis.*, 99: 511, 1944.
- ECKER, A. D. Hyaline change in basophil cells of pituitary body not associated with basophilism. *Endocrinology*, 23: 609, 1938.
- HEINBECKER, P., WHITE, H. L. and ROLF, D. Experimental obesity in dogs. *Am. J. Physiol.*, 141: 549, 1944.
- NEWBURGH, L. H. Obesity; energy metabolism. *Physiol. Rev.*, 24: 18, 1944.
- CONN, J. W. Obesity; etiological aspects. *Physiol. Rev.*, 24: 31, 1944.
- ALBRIGHT, FULLER. Cushing's syndrome. Harvey Lectures. Series 38, p. 123, 1942-1943.
- BROBECK, J. R. Mechanism of development of obesity in animals with hypothalamic lesion. *Physiol. Rev.*, 26: 541, 1946.
- HETHERINGTON, A. W. Production of hypothalamic obesity in rats already displaying chronic hypopituitarism. *Am. J. Physiol.*, 140: 89, 1943.
- RANSON, S. W., FISHER, C. and INGRAM, W. R. Adiposity and diabetes mellitus in monkey with hypothalamic lesions. *Endocrinology*, 23: 175, 1938.
- RASMUSSEN, A. T. Cited by Ranson et al.¹⁷
- GOLDZIEHER, J. W. Pituitary lesions accompanying obesity. *Arch. Path.*, 41: 203, 1946.
- RONY, H. R. Obesity and Leanness. Philadelphia, 1940. Lea & Febiger.
- COOPE, R. and CHAMBERLAIN, E. N. Effect of pituitrin on fatty acid of liver. *J. Physiol.*, 60: 69, 1925.
- HYND, A. and ROTTER, D. L. Studies on metabolism of animals on carbohydrate-free diet; effect of pitressin and pitocin on distribution of fat and glycogen in liver and muscles of albino rats. *Biochem. J.*, 26: 578, 1932.
- MUKERJI, B. and VAN DYKE, H. B. Effect of pressor principle of posterior lobe of pituitary body on liver fat after feeding of choline chloride. *Chinese J. Physiol.*, 9: 69, 1935.
- RAAB, W. Role of pituitary posterior hormone in fat metabolism. *Endocrinology*, 14: 385, 1930.
- RAAB, W. Die Beeinflussung des Fettstoffwechsels durch Hypophysenstoffe. *Klin. Wchnschr.*, 13: 281, 1934.
- VAN DYKE, H. B. Physiology and Pharmacology of the Pituitary Body. Chicago, 1936. Chicago University Press.

27. BLOTNER, H. Blood fat tolerance tests in malnutrition and obesity. *Arch. Int. Med.*, 55: 121, 1935.
28. HEINBECKER, P. and ROLF, D. Hypophyseal eosinophil cell and insulin sensitivity. *Am. J. Physiol.*, 141: 566, 1944.
29. WARREN, S. Pathology of Diabetes Mellitus. P. 194. Baltimore, 1930. Lea & Febiger.
30. McPHERSON, E. Case of diabetes mellitus, associated with lesions of pituitary body. *Glasgow M. J.*, 131: 220, 1939.
31. FRY, H. J. B. The pituitary gland in diabetes mellitus and disorders of the glands of internal secretion. *Quart. J. Med.*, 8: 277, 1915.
32. GLEN, A. Diabetes mellitus; broader basis of interpretation. *Glasgow M. J.*, 122: 194, 1934.
33. CAMUS, J., GOURNAY, J. J. and LEGRAND, A. Diabetes induced by nerve lesion. *Presse méd.*, 33: 249, 1925.
34. BARRIS, R. W. and INGRAM, W. R. Effect of experimental hypothalamic lesions upon blood sugar. *Am. J. Physiol.*, 114: 555, 1936.
35. MORGAN, L. O., VONDERAHE, A. R. and MALONE, E. F. Pathological changes in hypothalamus in diabetes mellitus; study of 15 cases. *J. Nerv. & Ment. Dis.*, 85: 125, 1937.
36. SHOCK, N. W. Metabolism in old age. *Bull. New York Acad. Med.*, 24: 166, 1948.
37. GILMAN, A. and GOODMAN, L. The Pharmacological Basis of Therapeutics; P. 666. New York, 1941. The Macmillan Co.
38. FISHER, C., INGRAM, W. R. and RANSOM, S. W. Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance. Ann Arbor, 1938. Edwards Bros.
39. HEINBECKER, P., WHITE, H. L. and ROLF, D. The essential lesion in experimental diabetes insipidus. *Endocrinology*, 40: 104, 1947.
40. MULINOS, C. L., SPRINGARN, C. L. and LOJIN, M. E. Diabetes insipidus-like condition produced by small doses of desoxycorticosterone acetate in dogs. *Am. J. Physiol.*, 135: 102, 1941.
41. SHANNON, J. A. Control of renal excretion of water; rate of liberation of posterior pituitary antidiuretic hormone in dog. *J. Exper. Med.*, 76: 387, 1942.
42. WINTER, C. A., INGRAM, W. R. and GROSS, E. G. Effects of pitressin injections upon serum electrolytes and water exchange of cats with diabetes insipidus and adrenal insufficiency. *Am. J. Physiol.*, 127: 64, 1939.
43. FINDLEY, T., JR. and WHITE, H. L. Response of normal individuals and patients with diabetes insipidus to ingestion of water. *J. Clin. Investigation*, 16: 197, 1937.
44. ROBINSON, F. J., POWER, M. H. and KEPLER, E. J. Two new procedures to assist in recognition and exclusion of Addison's disease; preliminary report. *Proc. Staff Meet., Mayo Clin.*, 16: 577, 1941.
45. GERSH, I. and GROLLMAN, A. Kidney function in adrenal cortical insufficiency. *Am. J. Physiol.*, 125: 66, 1939.
46. MARTIN, S. J., HERRLICH, H. C. and FAXEKAS, J. F. Relation between electrolyte imbalance and excretion of antidiuretic substance in adrenalectomized cats. *Am. J. Physiol.*, 127: 51, 1939.
47. BARD, P. Hypothalamus and sexual behavior. *A. Research Nerv. & Ment. Dis., Proc.*, 20: 551, 1939, 1940.
48. DEY, F. L. Evidence of hypothalamic control of hypophyseal gonadotropic functions in female guinea pig. *Endocrinology*, 33: 75, 1943.
49. BROOKS, C. M. Relation of hypothalamus to gonadotropic functions of hypophysis. *A. Research Nerv. & Ment. Dis., Proc.*, 20: 525, 1939, 1940.
50. DEMPSEY, E. W. and UOTILA, U. The effect of pituitary stalk section upon reproductive phenomena in the female rat. *Endocrinology*, 27: 573, 1940.
51. FOGLIA, V. G. El peso de los organos de la rata diabético. *Rev. Soc. argent. de biol.*, 21: 45, 1945.
52. WHITE, P. Pregnancy complicating diabetes. *J. A. M. A.*, 128: 181, 1945.
53. ALBRIGHT, FULLER. Osteoporosis. *Ann. Int. Med.*, 27: 861, 1947.
54. BRAUN-MENENDEZ, E. et al. Renal Hypertension. P. 298. Springfield, Ill., 1946. Charles C. Thomas.
55. VAN BOGAERT, A. and VAN BAARLE, F. Contribution à l'étude de l'hypertension artérielle dans ses rapports avec le système hypothalamo hypophysaire. *Cardiologia*, 5: 275, 1941.
56. BRUGER, M., ROSENKRANTZ, J. and LOWENSTEIN, B. Studies on the morphology of the adrenal cortex and on the excretion of 17-ketosteroids in hypertensive patients. *Am. J. M. Sc.*, 208: 212, 1944.
57. SELYE, F. L. Biochemical changes in hypertension. *Canad. M. A. J.*, 57: 325, 1947.
58. HAYNES, F. E., DEXTER, L. and SEIBEL, R. E. Renin content of renal venous blood of normal and hypertensive patients at rest. *Am. J. Physiol.*, 150: 198, 1947.
59. HULSE, W. Zur Frage der Blutdrucksteigerung. II. Untersuchungen über gefäßverengernde Stoff im Blute. *Ztschr. f. d. ges. Exper. Med.*, 30: 268, 1922.
60. RINEHART, J. F., WILLIAMS, O. O. and CAPELLER, W. S. Adenomatous hyperplasia of adrenal cortex associated with essential hypertension. *Arch. Path.*, 32: 169, 1941.
61. CASTLEMAN, B. and SMITHWICK, R. H. Relation of vascular disease to hypertensive state based on study of renal biopsies from 100 hypertensive patients. *J. A. M. A.*, 121: 1256, 1943.
62. RUSSI, S., BLUMENTHAL, H. T. and GRAY, S. T. Small adenomas of the adrenal cortex in hypertension and diabetes. *Arch. Int. Med.*, 76: 284, 1945.
63. SARASON, E. L. Adrenal cortex in systemic disease; morphologic study. *Arch. Int. Med.*, 71: 702, 1943.
64. NUZUN, F. R. and DALTON, J. W. Paroxysmal and persistent hypertension in association with lesions of the adrenal glands. *Am. Heart J.*, 16: 643, 1938.
65. DUBLIN, WILLIAM. Relation of structure of adrenal cortex to function in hypertension. *Northwest Med.*, 42: 263, 1943.
66. DEMPSEY, W. S. Adrenal cortex in essential hypertension. *Arch. Path.*, 34: 1031, 1942.

67. COMMONS, R. R. and CALLAWAY, C. P. Adenomas of the adrenal cortex. *Arch. Int. Med.*, 81: 37, 1948.
68. MELLGREN, J. The Anterior Pituitary in Hyperfunction of the Adrenal Cortex. Copenhagen, Ejnar Munksgaard. *Acta path. et microbiol. Scandinav.*, 1945.
69. PEDERSEN, A. H. and KENYON, T. J. Cushing's syndrome associated with fuchsinophilic staining reaction in the adrenal. *Surgery*, 22: 954, 1947.
70. SELYE, H. General adaptation syndrome and diseases of adaptation. *J. Clin. Endocrinol.*, 6: 117, 1946.
71. SELYE, H. and STONE, H. Pathogenesis of cardiovascular and renal changes which usually accompany malignant hypertension. *J. Urol.*, 56: 399, 1946.
72. FREEDMAN, S. M., POLLEY, J. R. and FRIEDMAN, C. L. The effect of desoxycorticosterone acetate on blood pressure, renal function, and electrolyte pattern in the intact rat. *J. Exper. Med.*, 87: 329, 1948.
73. BRAUN-MENENDEZ, E.⁵⁴
74. GOLDBLATT, H. Experimental renal hypertension. *Am. J. Med.*, 4: 100, 1948.
75. KNOWLTON, A. I., STOERCK, H. C., SEEGLER, B. C. and LOEB, E. N. Influence of adrenal cortical steroids upon blood pressure and rate of progression of experimental nephritis in rats. *Endocrinology*, 38: 315, 1946.
76. PERERA, G. A. Relationship of adrenal cortex to hypertension; observations on effect of hypoadrenalism on patient with hypertensive vascular disease. *J. A. M. A.*, 129: 537, 1945.
77. PERERA, G. A. and BLOOD, D. Disturbances in salt and water metabolism in hypertension. *Am. J. Med.*, 1: 602, 1946.
78. PERERA, G. A. and BLOOD, D. W. The relationship of sodium chloride to hypertension. *J. Clin. Investigation*, 26: 109, 1947.
79. PERERA, G. A. and BLOOD, D. W. Pressor activity of desoxycorticosterone acetate in normotensive and hypertensive subjects. *Ann. Int. Med.*, 27: 401, 1947.
- 79a. PERERA, G. A. Effect of continued desoxycorticosterone administration in hypertensive subjects. *Proc. Soc. Exper. Biol. & Med.*, 68: 248, 1948.
- 79b. PINES, K. L., PERERA, G. A., VISLOCKY, KATHERINE and BARROWS, ANN. Effort of adrenal cortical extract in hypertensive subjects. *Proc. Soc. Exper. Biol. & Med.*, 68: 268, 1948.
- 79c. GOLDMAN, M. L. and SCHROEDER, H. A. Immediate pressor effect of desoxycorticosterone acetate in arterial hypertension. *Am. J. Med.*, 5: 33, 1948.
80. SCHROEDER, H. A. Low salt diets and arterial hypertension. *Am. J. Med.*, 4: 578, 1948.
81. BARNETT, H. L., PERLEY, A. M. and HEINBECKER, P. Influence of eosinophilic cells of hypophysis on kidney function. *Proc. Soc. Exper. Biol. & Med.*, 52: 114, 1943.
82. WHITE, H. L., HEINBECKER, P. and ROLF, D. Some endocrine influences on renal function and cardiac output. *Am. J. Physiol.*, 149: 404, 1947.
83. WHITE, H. L., HEINBECKER, P. and ROLF, D. Endocrine influences on cardiac output and oxygen consumption in dogs. *Am. J. Physiol.*, 151: 239, 1947.
84. NORRIS, E. H. Arrhenoblastoma; malignant ovarian tumor associated with endocrinological effects. *Am. J. Cancer*, 32: 1, 1938.
85. DUGUID, J. B. and KENNEDY, A. M. Oat-cell tumors of mediastinal glands. *J. Path. & Bact.*, 33: 93, 1930.
86. LEYTON, O., TURNBULL, H. M. and BRATTON, A. B. Primary cancer of thymus with pluriglandular disturbance. *J. Path. & Bact.*, 34: 635, 1931.
87. SEVRINGHAUS, A. E. and THOMPSON, K. W. Cytological changes induced in hypophysis by prolonged administration of pituitary extract. *Am. J. Path.*, 15: 391, 1939.
88. KRAUS, E. J. Wie lässt sich die Annahme eines corticotropen Hyperpituitarismus beim Menschen morphologisch stützen? *Klin. Wchnschr.*, 16: 1528, 1937.
89. FINDLEY, T. Unpublished data.
90. SATTLER, D. G. and INGRAM, W. R. Experimental hypertension and neurohypophysis. *Endocrinology*, 29: 952, 1941.
91. DEBODO, R. and MARINE, D. The change in water metabolism and in the endocrine glands of long-surviving diabetes insipidus dogs. *Federation Proc.*, 5: 22, 1946.
92. WALTER, C. W. and PIJOAN, M. J. Persistent hypertension due to hypothalamic injury. *Surgery*, 1: 282, 1937.
93. FULTON, J. F. Physiology of the Nervous System. London, 1938. Oxford University Press.
94. RAGAN, C. et al. Syndrome of polydipsia and polyuria induced in normal animals by desoxycorticosterone acetate. *Am. J. Physiol.*, 131: 73, 1940.
95. COREY, E. L. and BRITTON, S. W. Antagonistic action of desoxycorticosterone and post-pituitary extract of chloride and water balance. *Am. J. Physiol.*, 133: 511, 1941.
96. ZIERLER, K. L. and LILIENTHAL, J. L., JR. Sodium loss in man induced by desoxycorticosterone acetate; study in a subject with myotonic dystrophy. *Am. J. Med.*, 4: 186, 1948.
97. LOEB, R. F. Adrenal cortex and electrolyte behavior. Harvey Lecture. *Bull. New York Acad. Med.*, 18: 263, 1942.
98. ANDERSON, J. A. and MURLIN, W. R. Antagonism of pitressin and adrenal cortical extract in human diabetes insipidus. *J. Pediat.*, 21: 326, 1942.
99. MCQUARRIE, I., ANDERSON, J. A. and ZIEGLER, M. R. Observations on antagonistic effects of posterior pituitary and cortico-adrenal hormones in epileptic subject. *J. Clin. Endocrinol.*, 2: 406, 1942.
100. WINTER, C. A., GROSS, E. G. and INGRAM, W. R. Serum sodium, potassium and chloride after suprarenalctomy in cats with diabetes insipidus. *J. Exper. Med.*, 67: 251, 1938.
101. SWINGLE, W. W., REMINGTON, J. W., HAYS, H. W. and COLLINGS, W. D. Effectiveness of priming doses of desoxycorticosterone acetate in protecting adrenalectomized dog against water intoxication. *Endocrinology*, 28: 531, 1941.

102. EVERSOLE, W. J., GAUNT, R. and KENDALL, E. C. Effect of adrenal steroids in water intoxication. *Am. J. Physiol.*, 135: 378, 1942.
103. SILVETTE, H. and BRITTON, S. W. Renal function in opossums and mechanism of cortico-adrenal and post-pituitary action. *Am. J. Physiol.*, 123: 630, 1938.
104. COREY, E. L., SILVETTE, H. and BRITTON, S. W. Hypophyseal and adrenal influence on renal function in rat. *Am. J. Physiol.*, 125: 644, 1939.
105. GERSH, I. Water metabolism; endocrine factors. *A. Research Nerv. & Ment. Dis., Proc.*, 20: 436, 1939, 1940.
106. SELYE, H. and HALL, C. E. Production of nephrosclerosis and cardiac hypertrophy in rat by desoxycorticosterone acetate overdosage. *Am. Heart J.*, 27: 338, 1944.
107. MRAZEK, R. Further study of the influence of activated sterols on blood pressure. *Federation Proc.*, 1: 61, 1942.
108. GROLLMAN, A., HARRISON, T. R. and WILLIAMS, J. Effect of various sterol derivatives on blood pressure of rat. *J. Pharmacol. & Exper. Therap.*, 69: 149, 1940.
109. ROBBARD, S. and FREED, S. C. Effect of desoxycorticosterone acetate on blood pressure of dog. *Endocrinology*, 30: 365, 1942.
110. BRISKIN, H. L., STOKES, F. R., REED, C. K. and MRAZEK, R. G. Effects of vitamin D and other sterols on blood pressure in rat. *Am. J. Physiol.*, 138: 385, 1943.
111. GAUDINO, N. M. Las suprarenales en la hipertension arterial nefrogena. *Rev. argent. soc. biol.*, 20: 470, 1944.
112. BRAUN-MENENDEZ, E. and FOGLIA, V. G. Influencia de la hipofisis sobre la presion arterial de la rata. *Rev. argent. soc. biol.*, 20: 556, 1944.
113. HEINBECKER, P., ROLF, D. and WHITE, H. L. Effects of extracts of hypophysis, thyroid and adrenal cortex on some renal functions. *Am. J. Physiol.*, 139: 543, 1943.
114. GOLDMAN, M. L. and SCHROEDER, H. A. The immediate pressor effect of desoxycorticosterone acetate in hypertensive and normotensive. *Federation Proc.*, 7: 41, 1948.
115. GOLDMAN, M. L. and SCHROEDER, H. A. The immediate pressor effect of desoxycorticosterone acetate. *Science*, 107: 272, 1948.
116. GAUNT, R. and HAYS, H. W. Life maintaining effect of crystalline progesterone in adrenalectomized ferrets. *Science*, 88: 576, 1938.
117. McKEOWN, T. and SPURRELL, W. R. Results of adrenalectomy in pregnant albino rat. *J. Physiol.*, 98: 255, 1940.
118. REYNOLDS, R. M. and ALLEN, W. M. Physiology of the corpus luteum; the comparative actions of crystalline progestin and crude progestin on uterine motility in unanesthetized rabbits. *Am. J. Obst. & Gynec.*, 30: 309, 1935.
119. FRIEDMAN, S. M. Effect of progesterone anesthesia on systemic blood pressure. *Proc. Soc. Exper. Biol. & Med.*, 46: 197, 1941.
120. SELYE, HANS. The pharmacology of steroid hormones and their derivatives. *Canad. Rev. de biol.*, 1: 577, 1942.
121. SELYE, HANS. On the production of malignant hypertension by chronic exposure to various damaging agents. *Canad. Rev. de biol.*, 2: 501, 1943.
122. PICKERING, G. W. and PRINZMETAL, M. Effect of renin on urine formation. *J. Physiol.*, 98: 314, 1940.
123. OSTER, K. A. and MARTINEZ, O. Water metabolism in hypertensive rats. *J. Exper. Med.*, 78: 477, 1943.
124. FRANKEL, D. B. and WAKERLIN, G. E. Excretion of urinary antidiuretic principle in renal hypertensive dogs. *Am. J. Physiol.*, 138: 465, 1943.
125. GOLDBLATT, H. Experimental hypertension induced by renal ischemia. Harvey Lecture. *Bull. New York Acad. Med.*, 14: 523, 1938.
126. LEITER, L. and EICHELBERGER, L. The relative hypertensive effects of "renin" on dogs with normal and abnormal renal circulation. *J. Clin. Investigation*, 18: 477, 1939.
127. LEITER, L. and EICHELBERGER, L. Studies on renin; duration of pressor effect of large doses in conscious normal and renally abnormal dogs. Observations on anesthetized and uremic dogs, and anaphylactic and pathological effects of pig renin. *J. Clin. Investigation*, 22: 11, 1943.
128. PAGE, I. H. Pressor response of normal and hypertensive dogs to renin and angiotonin. *Am. J. Physiol.*, 134: 789, 1941.
129. BRAUN-MENENDEZ, E.⁵⁴
130. OGDEN, E., PAGE, E. W. and ANDERSON, E. Effect of posterior hypophysectomy on renal hypertension. *Am. J. Physiol.*, 141: 389, 1944.
131. VERNEY, E. B. and VOGT, M. Experimental investigation into hypertension of renal origin with some observations on convulsive "uremia." *Quart. J. Exper. Physiol.*, 28: 253, 1938.
132. BROWN, G. M. and MAEGRAITH, B. G. Characteristics of circulation of hypertensive rabbits. *J. Physiol.*, 99: 304, 1941.
133. HEINBECKER, P. Role for surgeons in problem of essential hypertension. *Ann. Surg.*, 112: 1101, 1940.
134. JENSEN, J. Adrenalin test in hypertension. *Am. Heart J.*, 5: 763, 1930.
135. CLOUGH, P. W. Cardiovascular reaction to epinephrin; epinephrin sensitiveness in patients with hypertension. *Bull. Johns Hopkins Hosp.*, 31: 266, 1920.
136. KOEHLER, A. E., MARSH, N. and HILL, ELSIE. The effect of epinephrine injected intravenously at a constant rate in normal and hypertensive cases. *J. Biol. Chem.*, 119: 59, 1937.
137. GREEN, D. M., JOHNSON, A. D., LOBB, A. and CUSICK, G. The effects of adrenalin in normal and hypertensive patients in relation to the mechanism of sustained pressure elevations. *J. Lab. & Clin. Med.*, 33: 332, 1948.
138. MYLON, E., HORTON, F. H. and LEVY, R. P. Influence of epinephrine on vasoconstrictor action of kidney extracts. Influence of epinephrine on vasoconstrictive action of organ extracts. *Proc. Soc. Exper. Biol. & Med.*, 66: 375, 378, 1947.
139. LONG, C. N. H. The conditions associated with the secretion of the adrenal cortex. *Federation Proc.*, 6: 461, 1947.

140. PICKERING, G. W. Peripheral resistance in persistent arterial hypertension. *Clin. Sc.*, 2: 209, 1936.
141. PRINZMETAL, M. and WILSON, C. Nature of peripheral resistance in arterial hypertension with special reference to vasomotor system. *J. Clin. Investigation*, 15: 63, 1936.
142. STEAD, E. A., JR. and KUNKEL, P. Nature of peripheral resistance in arterial hypertension. *J. Clin. Investigation*, 19: 25, 1940.
- 142a. WILKINS, R. W. and EICHNA, L. W. Blood flow to forearm and calf; vasomotor reactions: role of sympathetic nervous system. *Bull. Johns Hopkins Hosp.*, 68: 425, 1941.
143. FARRIS, E. J., YEAKEL, E. H. and MEDOFF, H. S. Development of hypertension in emotional gray Norway rats after air blasting. *Am. J. Physiol.*, 144: 331, 1945.
144. WOLFF, H. G. Protective reaction patterns and disease. *Ann. Int. Med.*, 27: 944, 1947.
145. RUSKIN, A., BEARD, O. W. and SCHAFER, R. L. Blast hypertension. *Am. J. Med.*, 4: 228, 1948.
146. DIAZ, J. T. and LEVY, S. E. Studies on experimental hypertension in rats. *Am. J. Physiol.*, 125: 586, 1939.
147. OGDEN, E., COLLINGS, W. D., TAYLOR, A. N. and TRIPP, E. Production of neuro-hypertension by kidney. *Texas Rep. Biol. & Med.*, 4: 14, 1946.
148. BRAUN-MENENDEZ, E.⁵⁴
149. HAYNES, F. W., DEXTER, L. and SEIBEL, R. E. Renin content of renal venous blood of normal and hypertensive patients at rest. *Am. J. Physiol.*, 150: 198, 1947.
150. SHORR, E., ZWEIFACH, B. W., FURCHGOTT, R. F. and BAEZ, S. Hepato-renal vasotropic factors in experimental shock and renal hypertension. *Tr. A. Am. Physicians*, 60: 28, 1947.
151. SHORR, E. Participation of hepatorenal vasotropic factors in experimental renal hypertension. *Am. J. Med.*, 4: 120, 1948.
152. GRIFFITH, J. Q., PADIS, N. and ANTHONY, E. Selection of patients with arterial hypertension for treatment by repeated injections of pitressin. *Am. J. M. Sc.*, 212: 31, 1946.

ADDENDUM

Additional pertinent references have appeared. By an entirely different technique Keller (KELLER, A. D. Experience in attempting to elucidate certain of the multitudinous functions of the pituitary gland,

using the experimental surgical approach. *Texas Rep. Biol. & Med.*, 6: 275, 1948) secured evidence that total hypophysectomy is not followed by adrenocortical atrophy if the hypothalamus is also injured and suggested that the hypothalamus creates a "contra-adrenotropic" hormone. Further evidence that the neurohypophysis and the adrenal cortex act in opposing directions is supplied by the report that adrenalectomy increases the concentration of antidiuretic substance in the blood of rats (BIRNIE, J. H., JENKINS, ROSEMARY, EVERSOLE, W. J. and GAUNT, R. An antidiuretic substance in the blood of normal and adrenalectomized rats. *Proc. Soc. Exper. Biol. & Med.*, 70: 83, 1949). Shaken and Greene (SHAKEN, J. G. and GREEN, D. M. Mechanisms of desoxycorticosterone action, relationship of fluid intake and pressor responses to output of antidiuretic factor. *Am. J. Physiol.*, 155: 290, 1948) found that DOCA given subcutaneously to rats caused polydipsia, hypertension and increased output of antidiuretic substance in the urine. Friedman and co-workers (FRIEDMAN, S. M., POLLEY, J. R. and FRIEDMAN, C. L. The effect of desoxycorticosterone acetate on blood pressure, renal function and electrolyte pattern in the intact rat. *J. Exper. Med.*, 87: 329, 1948) reported that DOCA pellets implanted in normal rats produced hypertension, constriction of efferent glomerular arterioles and a rise in plasma sodium. Patients with essential hypertension are hypersensitive to nor-epinephrine (GOLDENBERG, M., PINES, K. L., BALDWIN, ELEANOR DE F., GREENE, D. F. and ROH, C. E. The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. *Am. J. Med.*, 5: 792, 1948).

Seminars on Antibiotics

Origin and Nature of Antibiotics*

SELMAN A. WAKSMAN
New Brunswick, New Jersey

ANTIBIOTICS are chemical substances which are produced by micro-organisms and which have the capacity to inhibit the growth of and even to destroy bacteria and other micro-organisms. They are characterized by certain

upon true fungi; others attack both fungi and bacteria; still others act only upon fungi. Some are also active against rickettsiae and a few of the larger viruses. Some antibiotics possess antiprotozoan activities, affecting trypanosomes or trichomonads.

TABLE I
TYPICAL ANTIBACTERIAL SPECTRA OF SEVERAL ANTIBIOTICS—UNITS OF ACTIVITY PER 1 GM.
OF PREPARATION

Test Organism	Penicillin*	Actinomycin	Streptomycin	Clavacin
<i>B. subtilis</i>	19,000,000†	60,000,000	2,000,000	
<i>S. aureus</i>	9,500,000†	20,000,000	2,000,000	200,000
<i>S. lutea</i>	38,000,000†	60,000,000	4,000,000	100,000
<i>Cl. welchii</i>	1,500,000‡	1,000,000	125,000§	500,000
<i>B. anthracis</i>	1,000,000‡	2,500,000	
<i>Pr. vulgaris</i>	4,000‡	500,000	
<i>Br. abortus</i>	2,000‡	10,000	500,000	
<i>E. coli</i>	<1,000	5,000	1,000,000	100,000
<i>S. schottmülleri</i>	<1,000	<10,000	500,000	60,000
<i>M. tuberculosis</i>	<1,000	7,000,000	
<i>K. pneumoniae</i>	<1,000	1,000,000	
<i>S. marcescens</i>	<1,000	<5,000	1,000,000	60,000

* Considerable variation is found among different strains of the same organisms. Two crude preparations of penicillin used in these tests designated either by † or by ‡.
§ *Cl. butyricum* used.

distinct physical, chemical and biological properties which make them ideal potential chemotherapeutic agents. These can be described briefly as follows:

1. Antibiotics are highly selective in their action upon different micro-organisms. This selectivity extends not only to genera and species but even to strains and individual cells. Some antibiotics attack mainly gram-positive bacteria and only to a limited extent the gram-negative forms; others affect alike various types of bacteria within each of these two groups. Some have no effect

No antibiotics that are active against the smaller viruses have so far been isolated although the indications are that such exist. The variations in the action of antibiotics upon different bacteria and other micro-organisms are both qualitative and quantitative in nature. This suggested the concept of an "antibiotic spectrum," which records the selective action of a given antibiotic upon a number of representative bacteria and other micro-organisms. This is illustrated in Tables I and II.

2. The antibiotics represent a large num-

* From the Department of Microbiology, New Jersey Agricultural Experiment Station, Rutgers University, New Brunswick, N. J.

ber of chemical compounds, ranging from simple substances containing only C, H and O, to more complex forms which contain nitrogen, sulfur and even chlorine, as shown in Table III. They vary greatly in chemical structure as shown in the accompanying

from one another in the presence or absence of certain chemical groups. This may affect their quantitative activity upon different bacteria. This is true, for example, of the penicillins or the streptomycins. The various compounds within each antibiotic complex

TABLE II
TYPICAL ANTIBIOTIC SPECTRA OF SEVERAL ANTIBIOTICS PRODUCED BY DIFFERENT MICRO-ORGANISMS³—
MINIMUM INHIBITORY CONCENTRATION OF ANTIBACTERIAL SUBSTANCES IN MICROGRAMS PER ML.

Antibacterial Substance	B. mycoides	B. subtilis	S. aureus	E. coli	K. pneumoniae	P. aeruginosa	M. phlei
Aspergillilic acid . . .	2	4	4	62	13	1,000	125
Biformin	13	0.04	0.3	1.7	1.7	53	0.6
Citrinin	32	16	16	>1,000	125
Dihydrostreptomycin	0.25	0.5	0.03	0.25	0.13	4	0.25
Gliotoxin	0.25	0.25	0.15	25	6	500	4
Helvolic acid (fumigacin).	4	16	1	>1,000	4	>32
Kojic acid	2,500	620	1,250	2,500	620	5,000	2,500
Mycophenolic acid	500	250	250	500	>1,000	>1,000	500
Patulin (clavacin)	16	4	8	8	8	125	16
Penicillic acid	32	8	16	64	64	1,000	64
Penicillin G	30	0.03	0.016	14	110	500	14
Penicillin X	30	0.06	0.03	14	240	500	29
Pleurotin	3	0.2	0.8	>500	>500	>32
Spinulosin	125	125	63	250	250	500	250
Streptomycin	0.13	0.25	0.03	0.25	0.13	4	0.25
Streptothricin	100	0.8	0.1	0.3	0.1	2	7

structural formulas. Some of the antibiotics comprise several compounds which differ

TABLE III
CHEMICAL COMPOSITION OF CERTAIN ANTIBIOTIC SUBSTANCES

i. Compounds containing C, H and O:	
Kojic acid	C ₆ H ₆ O ₄
Clavacin	C ₇ H ₆ O ₄
Penicillic acid	C ₈ H ₁₀ O ₄
Pyolipic acid	C ₁₀ H ₂₀ O ₂
Gladiolic acid	C ₁₁ H ₁₆ O ₅
Mycophenolic acid	C ₁₂ H ₂₀ O ₆
Viridin	C ₂₀ H ₁₆ O ₆
Fumigacin, helvolic acid	C ₃₂ H ₄₄ O ₅
ii. Compounds containing C, H, O and N:	
Hemipyocyanin	C ₁₂ H ₅ ON ₂
Aspergillilic acid	C ₁₂ H ₂₀ O ₂ N ₂
Pyocyanin	C ₁₃ H ₁₀ ON ₂
Streptomycin	C ₂₁ H ₂₇₋₃₃ O ₁₂ N ₇
Pyo II	C ₃₄ H ₄₆ O ₄ N ₂
Actinomycin	C ₄₁ H ₅₆ O ₁₃ N ₈
Polypeptides—Gramicidin, tyrocidine, etc.	
iii. Compounds containing C, H, O, N and S:	
Penicillin	C ₉ H ₁₁ O ₄ SN ₂ ·R
Gliotoxin	C ₁₃ H ₁₄ O ₄ S ₂ N ₂
iv. Compounds containing chlorine:	
Ustin	C ₁₅ H ₁₅ O ₅ Cl ₂
Chloromycetin	
Aureomycin	

are produced by different strains of a given organism, by different organisms or by the same organism under different conditions of culture.

3. Certain micro-organisms are capable of producing more than one antibiotic. The ability of *Pseudomonas aeruginosa* to form pyocyanase, pyocyanin and hemipyocyanin has long been known; to these have recently been added the pyo-compounds, pyolipic acid and certain others. *Bacillus subtilis* forms a number of polypeptides which possess antibiotic properties; it is sufficient to mention bacitracin, subtilin and bacillin. *Aspergillus flavus* produces aspergillilic acid and certain forms of penicillin. *A. fumigatus* yields at least four antibiotics, namely, spinulosin, fumigatin, fumigacin and gliotoxin and possibly others. *Streptomyces griseus* forms the antibacterial agents streptomycin and mannosidostreptomycin, the antifungal agent actidione and the antitrichomonas agent streptocin; other strains of *S. griseus*

produce grisein and other antibiotics. Various strains of *S. lavendulae* are able to yield streptothricin, lavendulin, streptin, streptolin and others. The culture filtrates of some of the antibiotic-producing organisms are also active against various bacterial toxins whereas the purified antibiotics do not possess that activity; this phenomenon has been designated as the *antidotic effect*.

4. Some antibiotics are produced by several different organisms. The various penicillins are formed by *P. notatum*, *P. chrysogenum*, *A. flavus*, *A. giganteus*, *P. crustaceum* and a number of other fungi. The same is true of gliotoxin, clavacin and various other antibiotics. Clavacin is known under a number of different names, depending on the organism from which it was isolated. This accounts for "claviformin," "patulin," "clavatin," "expansin" and "leucopin." Actinomycin is produced by a large number of different actinomycetes belonging to the genus *Streptomyces*. Streptomycin has been isolated from cultures of *S. griseus* and *S. bikiniensis* and from cultures of organisms that are also able to form other antibiotics, such as streptothricin.

5. The nature of the substrate in which the antibiotic exerts its antibacterial effect may influence the nature and extent of this effect. Certain constituents of the medium reduce the activity of an antibiotic by neutralizing its action or by adsorbing or by inactivating the antibiotic. This is particularly true of the effects of salts and serum proteins, which may thus explain the differences in the *in vitro* vs. *in vivo* activities of certain antibiotics.

6. Some antibiotics, such as penicillin, are readily destroyed by various micro-organisms whereas others, such as streptomycin, are highly resistant to microbial action.

7. The mode of action of antibiotics upon bacteria varies. Some interfere with the growth of bacteria and with their cell division; some influence microbial respiration; others affect the utilization of essential metabolites by the bacteria.

8. Antibiotics vary greatly in their toxicity to animals. Some, like actinomycin and

xanthomycin, are extremely toxic; others, like penicillin, have virtually no toxicity at all; most of the other antibiotics fall between these two extremes. The specific effect of an antibiotic upon the various animal tissues also varies greatly.

9. Some antibiotics can be modified chemically so as to reduce their toxic properties. This is true of dihydrostreptomycin which is a reduced form of streptomycin.

10. Bacteria sensitive to a given antibiotic may gradually develop resistance to it when allowed to be in contact with it for some time. Different antibiotics vary greatly in this respect. Some, like streptomycin, allow rapid development of resistance of most bacteria originally sensitive to it; others, like penicillin, allow only gradual development of resistance of very few sensitive bacteria. The process of re-acquirement of sensitivity or loss of resistance also differs with the antibiotic and with the bacteria. A given bacterial culture may contain one or more cells far more resistant to a certain concentration of an antibiotic than the great majority of the cells in that culture; when these resistant cells develop, they give rise to a culture which shows far greater resistance to the particular antibiotic than the original culture.

Because of these differences in chemical properties, antibacterial activities and effect upon body tissues, antibiotics vary greatly in their chemotherapeutic potentialities. This is largely the reason why of more than one hundred antibiotics that have already been isolated and described, only five or six have so far found practical application in the treatment of infectious diseases.

HISTORICAL BACKGROUND

In tracing the historical development of our concepts of the nature and utilization of antibiotics, three distinct periods must be recognized: (1) The early observations of the growth of micro-organisms in mixed cultures, the effects of one organism upon another when grown in artificial media and the interactions among various organ-

isms found in a natural environment including mixed infections. (2) The first attempts to isolate, from pure cultures of bacteria and other micro-organisms, crude preparations or purified chemical substances which possessed antibacterial properties; these attempts were often accompanied by efforts to utilize the isolates for the control of infectious diseases. (3) The last decade when antibiotics became recognized as important chemotherapeutic agents and their role in the treatment of numerous diseases became permanently established.

To illustrate further these distinct phases in the history of a new branch of science, that of the science of antibiotics, a few additional facts may be cited:

Early Observations. From the early days of bacteriology it was recognized that various micro-organisms are capable of repressing, in culture, the growth of other organisms. Mixed infections were found to behave differently from the same type of infections caused by single disease-producing agents; in such mixed infections some of the organisms were able to repress the growth of others. An attempt was made to utilize such organisms, as in the treatment of infections by less pathogenic organisms, such as anthrax with streptococci or with *Ps. aeruginosa*.

Early students of the microbiologic population of the soil observed that the great majority of disease-producing organisms which find their way into the soil gradually tend to disappear there. This was shown to be due largely to the presence in the soil of microbes, known as antagonists, which brought about destruction of the disease-producing forms.

Those sporadic attempts that were made to utilize for chemotherapeutic purposes either the saprophytic organisms themselves or the chemical substances that they produced in culture media failed completely or at best yielded rather inconclusive results. This was due, partly at least, to an insufficient differentiation between the activities of the living organisms and of their

chemical products which possessed antibacterial properties.

The evidence submitted in support of these isolated observations did not exert any profound influence upon the understanding of the mechanism of disease or upon the course of medical practice. Although many of these studies were fundamental in nature, the results obtained did not fit into a well coordinated pattern. They certainly did not point to the great potentialities in the field of utilization of antibiotics for disease control as it is visualized today. Without reviewing in detail the numerous observations in this field, a few illustrations will suffice:

In 1885 Cantani attempted to utilize certain common bacteria for the treatment of tuberculosis. Cultures of the saprophyte of doubtful purity were blown into the lungs of the patients. A certain improvement in their condition resulted; this was accompanied by the appearance of the saprophytic organism in the sputum. Emmerich demonstrated somewhat later that an injection of streptococci into animals enabled them to withstand infection from *B. anthracis*. Bouchard also showed that inoculation of animals with *Ps. aeruginosa* gave protection against anthrax.

The replacement of pathogenic bacteria in a given infection by saprophytic organisms or by potentially lesser pathogens forms a most interesting chapter in the history of microbiology and medical practice. Introduction into the human intestines of harmless lactic acid organisms to replace potentially dangerous enteric bacteria was initiated by Metchnikov and later found wide application. The use of *Escherichia coli* for the purpose of replacing pathogenic bacteria in the gut was first postulated by Nissle in 1916; this was the vogue for awhile. In the treatment of diphtheria recourse was had to use of several bacteria, ranging from lactic acid organisms to *Staphylococcus aureus*; the resulting effects were not always too favorable to the host, as one might expect from an excessive application of *S. aureus*. Use of various forms of yeasts, by different

methods of administration, also had a certain popularity at one time, again with rather uncertain results. Cultures of lactobacilli were used not only for internal but also for external administration, as in the treatment of vaginal trichomoniasis. Application of cultures of *Lactobacillus acidophilus* was said to be beneficial in the treatment of various forms of diarrhea and dysentery.

The first attempt to use an antibiotic preparation must be credited to Emmerich and Löw who, in 1899, utilized pyocyanase for combating infections. This was followed by numerous other efforts of a similar nature. The results obtained were rather uncertain and often disappointing in spite of the fact that at times some favorable indications were obtained. Pyocyanase preparations appeared to find special application in surface therapy; they were used clinically in a number of infections, including nasal sinuses, Vincent's angina, diphtheria and, in veterinary practice, streptococcal mastitis.

Fungus products as well were tried for their clinical potentialities. In 1913, Vaudremer, for example, used the metabolic products of *A. fumigatus* for combating tuberculosis; although some 200 patients were thus treated, the results were again rather inconclusive. Gratia utilized cultures of certain actinomycetes for the purpose of lysing typhoid bacteria; the preparations thus obtained were designated as *mycolysates* and were used for immunizing purposes.

A number of other microbiologic preparations were tested for their therapeutic power. Frequently the total culture filtrate of the organisms was used. These preparations were occasionally found to possess marked antibacterial properties. Some of them were active against bacteria not only in the test tube but also in experimental animals. A few of them were even used clinically, with varying degrees of success, in the treatment of various human infections, such as anthrax, diphtheria and tuberculosis. The results obtained from these investigations were not sufficient, however,

to warrant drawing broad conclusions concerning the possibility of utilizing the metabolic products of micro-organisms as chemotherapeutic agents, except under varied special conditions and upon a limited number of infections.

First Isolation of Antibiotics. Among the three major groups of micro-organisms largely responsible for the production of antibiotics at the present time, namely, the bacteria, fungi and actinomycetes, the first received the earliest consideration. The ability of certain bacteria belonging to the pyocyanus group to inhibit the growth of and even to kill other bacteria was investigated nearly six decades ago. This organism yielded a preparation designated as *pyocyanase*, which may be considered as the first antibiotic ever isolated and described. This ability of certain bacteria to yield substances that possessed antibacterial properties was considered to be a freak and was not visualized as having a widespread distribution among micro-organisms. Pyocyanase was actually believed to be an enzyme system that had the capacity of bringing about lysis of certain bacterial cells.

A mere review of the voluminous literature on the compounds possessing antibacterial properties which have been isolated from the culture medium and from the cells of *Ps. aeruginosa* would take far more space than would be justified in this brief summary of the field of antibiotics. Suffice to say that even at the present time, after more than half a century of research, this organism and its characteristic capacity of causing inhibition of bacterial growth still continue to attract the attention of many investigators. Attention is directed only to the recent work of Doisy and his associates on the pyo-compounds and of Bergström, Theorell and Davide on pyolipic acid. Although numerous claims have been made concerning the practical application of some of the preparations obtained from this organism, none of these preparations has so far become established as a recognized chemotherapeutic agent.

The isolation of antibiotics from spore-forming bacteria also covers extensive literature. It is sufficient to draw attention to the earlier work of Nicolle, Pringsheim and Much, on specific organisms belonging to the *B. subtilis*, *B. mesentericus* and *B. mycoides* groups, and to numerous other investigations on the ability of various other spore-forming bacteria to inhibit the growth of bacteria and other micro-organisms, including many human and animal pathogens. These studies culminated in 1939 in the work of Dubos, who isolated from cultures of the *B. brevis* group a series of polypeptides which possessed remarkable antibacterial properties. The *tyrothricin* complex contained two crystalline compounds, *gramicidin* and *tyrocidine*. This was followed by a survey of numerous other products of spore-forming bacteria, some of which appear to possess remarkable properties of promising chemotherapeutic agents.

The ability of fungi to inhibit the growth of other micro-organisms was also recognized before the end of the last century. Gosio is credited with having isolated from a culture of *Penicillium* an antibiotic substance designated as *mycophenolic acid*. These early studies were followed by the work of Duchesne and Vaudremer, to be culminated in the work of Fleming in 1929, who isolated from a culture of *Penicillium notatum* a preparation designated as *penicillin* which possessed remarkable antibacterial properties. More than a decade elapsed, however, before Florey, Chain and their associates demonstrated, in 1940 to 1941, its remarkable chemotherapeutic properties. This was soon followed by a deluge of investigations on the production of penicillin, as well as on the general subject of the production of antibiotic substances by fungi. One other antibiotic isolated during the early period must be mentioned here, namely, gliotoxin. Although this agent was crystallized and its antifungal properties were established, its antibacterial activities were not recognized. Certain other products of fungus metabolism were isolated by Raistrick and his collaborators, but the antibacterial poten-

tialities of these products were not established until later.

Although various observations have been made in the past concerning the ability of certain actinomycetes to inhibit the growth of bacteria, the comprehensive study of the formation of antibiotics by this group of organisms dates only to the last decade. The two outstanding groups of investigations previous to 1939 are: first, those of Gratia and Welsch on the production of a lytic system by an organism designated first as *streptothrix* and later as *Actinomyces albus*, the active agent finally being named *actinomycin* and, second, the surveys of several Russian investigators on the occurrence of antagonistic actinomycetes in the soil and their selective action upon various bacteria. The systematic investigation of the production of antibiotics by actinomycetes, begun in 1940 by the workers of the Department of Microbiology of the New Jersey Agricultural Experiment Station and which resulted in the isolation of actinomycin, micromonosporin, streptothricin, streptomycin, grisein, streptocin and neomycin, gave a marked stimulus to the study of these organisms, with the result that more than thirty compounds have now been isolated. These vary greatly in their chemical nature, antimicrobial spectra, toxicity to animals and chemotherapeutic potentialities.

The production of antibiotic substances may thus be considered as a phenomenon widely distributed among micro-organisms. The nature of the antibiotic and its quantitative yield depend upon the organism, the manner of its nutrition and conditions of growth. One type of antibiotic may be produced by a certain organism grown in surface culture and another type under submerged conditions. *A. flavus*, for example, produces largely aspergillic acid in stationary culture and flavicin, a penicillin-like substance, produces the acid in submerged culture. The nutrition of *B. brevis* and the production of tyrothricin by this organism are quite different under submerged conditions of growth as compared to stationary cultures. Certain organisms require specific

nutritional or growth-promoting agents or precursors for the formation of a given substance; other antibiotics are produced in synthetic or simple organic media.

Attempts have been made to explain the capacity of antagonistic micro-organisms to produce antibiotics on the basis of their struggle for existence in nature. The available evidence does not fully justify this assumption. Although the presence in the soil of certain toxic compounds, which may be classified with the antibiotics, has been demonstrated, no evidence has as yet been submitted to prove that the accumulation or even the formation by micro-organisms of antibiotics under soil conditions is based upon competition for either nutrients or space.

The available evidence leads to the conclusion that various micro-organisms have the inherent capacity of inhibiting the growth of or killing other organisms. This is usually brought about by the formation of specific chemical agents, namely, antibiotics. Such properties may or may not be stimulated by the addition to the substrate of sensitive organisms. The ability to produce antibiotics may be due to strain selectivity of the organism, to improvement in the culture medium for its development or to stimulation of a latent capacity which it possesses.

The Last Decade. To bring all these cursory observations together into one system and thus lay the groundwork for the science of antibiotics, and especially to determine their potentialities as chemotherapeutic agents, a synthesis was needed. This required the coordinated efforts of the microbiologist, chemist, pharmacologist and clinician in order to test various cultures of micro-organisms obtained from different substrates for their ability to inhibit bacterial growth and produce antibiotic substances, to isolate such substances from the metabolite solution, to evaluate their toxicity and effectiveness in the animal body and finally to test them clinically. This synthesis was brought about in 1939 to 1940, when isolation of tyrothricin, soon followed

by the re-isolation of penicillin, established beyond doubt that substances of microbial origin, the antibiotics, can find an important place in chemotherapy, not only of human diseases but also of animal and possibly even of plant diseases.

It is of special interest to draw attention to the fact that three groups of investigations, which have thus laid the foundation for the recent advances in our knowledge of antibiotics, dealt with the three groups of micro-organisms that are now considered to be the most important producers of antibiotic substances. (1) Investigation of the tyrothricin complex produced by *B. brevis*. This not only served to focus attention upon an important group of antibiotics, the bacterial polypeptides, but also laid the foundation for extensive studies of aerobic spore-forming bacteria. This led to the isolation of a large number of compounds, designated as *gramicidin S*, *subtilin*, *bacitracin*, *licheniformin*, *polymyxin*, *aerosporin*, *bacillin*, *eumycin*, *subtilysin*, *endosubtilysin* and others. (2) The work on the penicillin complex. This was followed by numerous studies on the production of antibiotics by fungi, with major emphasis on the various forms of penicillin. These studies resulted in isolation of a large number of antibiotics, including *aspergillin*, *aspergillic acid*, *citrinin*, *clavacin* (*claviformin*, *patulin*), *fumigacin* (*gladiolic acid*), *glutinosin*, *javanicin*, *mycoidin* and penicillin-like substances. With the exception of penicillin, none of the fungus antibiotics has so far shown any outstanding promise as a chemotherapeutic agent. (3) Investigation of the production of antibiotics by actinomycetes. This resulted first in the isolation in 1940 of actinomycin—a highly toxic compound. Others followed, most important of which are, in order of isolation, *streptothricin*, *streptomycin*, *chloromycetin*, *aureomycin* and *neomycin*, several of which proved to be highly important chemotherapeutic agents. A large number of other antibiotics have been isolated from cultures belonging to this group, such as *micromonosporin*, *nocardin* and *proactinomycin*.

WHAT ANTIBIOTICS ARE DESIRABLE?

It is now generally recognized that for a new antibiotic to qualify as a chemotherapeutic agent it must satisfy certain definite requirements, the most important of which may be summarized briefly as follows: (1) It must be selective in its action against various groups of micro-organisms and should not be a generalized protoplasmic poison. (2) It must have desirable antibacterial properties, that is, it must affect bacteria or other micro-organisms that are not subject to the action of other antibiotics or synthetic chemical compounds, or it must be more potent or more effective than others which it is to replace. (3) It must be active in the presence of body fluids. (4) It must not be destroyed by tissue enzymes. (5) It must not be toxic, or at least not too toxic to animals as a whole, or to individual cells, such as leukocytes, or to tissues, such as kidneys. (6) Preferably it should possess desirable physical and chemical properties, such as solubility in water and a certain degree of stability. (7) It should be excreted readily, but not too rapidly, from the animal system and should not accumulate there and produce undesirable after-effects.

Some of the more interesting antibiotics, even if not always the most desirable, may now be discussed in somewhat greater detail.

ANTIBIOTICS OF BACTERIA

Large numbers of bacteria, including gram-positive and gram-negative forms, spore-forming and non-spore-forming cocci and bacilli, have the capacity of producing antibiotics. Some of these substances are active largely upon gram-positive bacteria; some are active also upon gram-negative forms; some are able to attack fungi. A few of them have found application as chemotherapeutic agents. Only some of these need be considered in further detail.

Tyrothricin is made up of about 20 to 25 per cent gramicidin and 60 per cent tyrocidine. The first is a large polypeptide, having a molecular weight of about 2,826, with a high content of tryptophane and cer-

tain natural and unnatural isomers of other amino acids. It is insoluble in water and is active only against gram-positive bacteria both *in vitro* and *in vivo*. Tyrocidine has a molecular weight of 2,564 and is composed of *l*-amino acid residues and 3 residues of *d*-phenyl alanine. It is active against various bacteria only *in vitro*. It is inhibited by serum proteins.

Polymyxin is a basic substance soluble in water. It is highly active against various gram-negative bacteria, both *in vitro* and *in vivo*; its activity is not affected by the reaction of medium within a range of pH 5 to 8. It appears to be identical with a similar antibiotic described as *aerosporin*.

Bacitracin is produced by a member of the *B. subtilis* group. It is a neutral compound, soluble in water and in organic solvents. Its polypeptide nature has recently been questioned. It is highly active against certain gram-positive bacteria, has limited toxicity in animals and clinically exerts a marked effect in the treatment of infections caused by sensitive bacteria.

Subtilin is produced by a strain of *B. subtilis*. It is insoluble in 95 per cent alcohol but is soluble in 70 per cent. It is active only against gram-positive bacteria, including *M. tuberculosis*, both *in vitro* and *in vivo*. It is also active against a number of pathogenic fungi, *Endamoeba histolytica* and *Trypanosoma equiperdum*. Its low toxicity and *in vitro* activity make it a potential chemotherapeutic agent.

Licheniformin was isolated from *B. licheniformis*, a strain of *B. subtilis*. It is not active against gram-negative bacteria but is effective against certain gram-positive forms, including *M. tuberculosis*.

Nisin is produced by certain lactic acid streptococci. It is active, both *in vitro* and *in vivo*, against various gram-positive bacteria, including *M. tuberculosis*. It is similar in many respects to *diplococcin*, another antibiotic produced by lactic acid cocci, a protein-like material of small molecular weight.

Colicins are a group of antibiotics produced by certain strains of *Escherichia coli*

and other enteric bacteria. They are highly specific in their action upon other enteric bacteria, species of *Shigella* being most sensitive. The various colicins differ in their antibiotic spectra and in their physiochemical properties. Some cultures produce several colicins with different antibiotic spectra. They are peptides in nature and are destroyed by proteolytic enzymes; they are soluble in water, insoluble in organic solvents and heat-stable. Their potential chemotherapeutic value is questionable.

Pyo-compounds are extracted from the cells of *Ps. aeruginosa* with hot alcohol. They are nitrogenous compounds ($C_{34}H_{46}N_2O_4$ etc.) and are active against gram-positive bacteria, apparently *in vitro* only.

Pyolipic acid has also been obtained from *Ps. aeruginosa*. It has the composition of $C_{11}H_{22}O_3$ and is active against *M. tuberculosis*.

Numerous other bacteria were found to have the capacity of producing antibiotic substances but most of them, as in the case of marine bacteria, have been but little studied.

ANTIBIOTICS OF FUNGI

Fungi form by far the largest group of organisms which have the capacity to produce antibiotics. Some of the earliest and some of the most recent compounds have been isolated from this group of microorganisms. Very few of the *Phycomycetes* yielded any antibiotics. Only one preparation active against *Tr. equiperdum* was reported. It is soluble in organic solvents and in water. The *Basidiomycetes* have yielded a number of compounds, some of which, notably *polyporin* and *clitocibin*, were believed to offer potentialities as chemotherapeutic agents, the latter against *M. tuberculosis*. Certain agarics were also found to have a marked effect upon this organism. The pigment lactaroviolin is active in very low concentrations. Some of the antibiotics isolated from lichens, such as *usnic acid* and *ramularin*, have also been found to be highly effective against the tubercle organism not only *in vitro* but also *in vivo*.

The largest number of antibiotics have

been isolated from *Hyphomycetes*. Some of these are toxic and offer, therefore, little promise of becoming chemotherapeutic agents; the potentialities of others have still been little investigated. Among the more important antibiotics the *penicillins* occupy the leading place. Although the greatest interest is manifested in the clinical application of penicillins, considerable knowledge has been gained of the physiology of *P. notatum* and *P. chrysogenum* and the biochemical problems concerned in penicillin production and the mode of action of penicillin upon bacteria. Various species of *Aspergillus* have also been found to produce penicillin. In addition some form other antibiotics, such as *aspergillic acid*.

Only a few of the antibiotics produced by fungi are described in detail herein.

Penicillin. At least six closely related compounds comprise the penicillin group. They are produced by a number of fungi, chiefly members of the *P. notatum-chrysogenum* groups. They are active largely against gram-positive bacteria and have little activity against gram-negative rods and acid-fast bacteria, fungi or viruses. The penicillins are relatively non-toxic and have found extensive application in chemotherapy, notably in diseases caused by cocci (staphylococci, gonococci, meningococci), gram-positive rod-shaped bacteria, including both aerobic and anaerobic forms, and spirochaetes.

Clavacin. Clavacin is active against various gram-positive and gram-negative bacteria, acid-fast bacteria and fungi. It is very toxic to both animals and plants and therefore has not found any practical application.

Fumigacin (helvolic acid). Fumigacin is produced by various strains of *Aspergillus fumigatus*, an organism capable of producing a variety of other antibiotics, notably *gliotoxin*, *fumigatin*, *spinulosin* and an anti-tumor factor. It is soluble in organic solvents and insoluble in water. It mainly inhibits gram-positive bacteria. It is fairly toxic and has found no application in chemotherapy.

Gliotoxin. Gliotoxin is produced by a number of fungi. It is soluble in organic

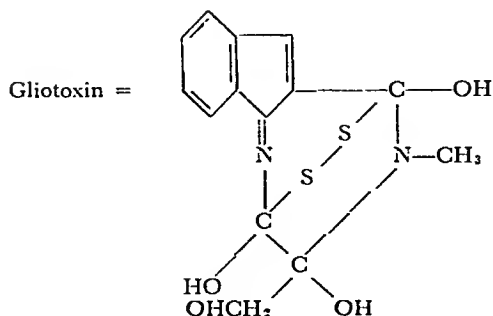
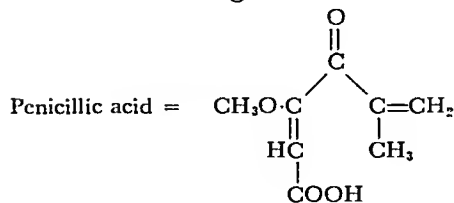
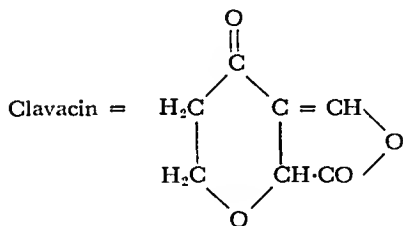
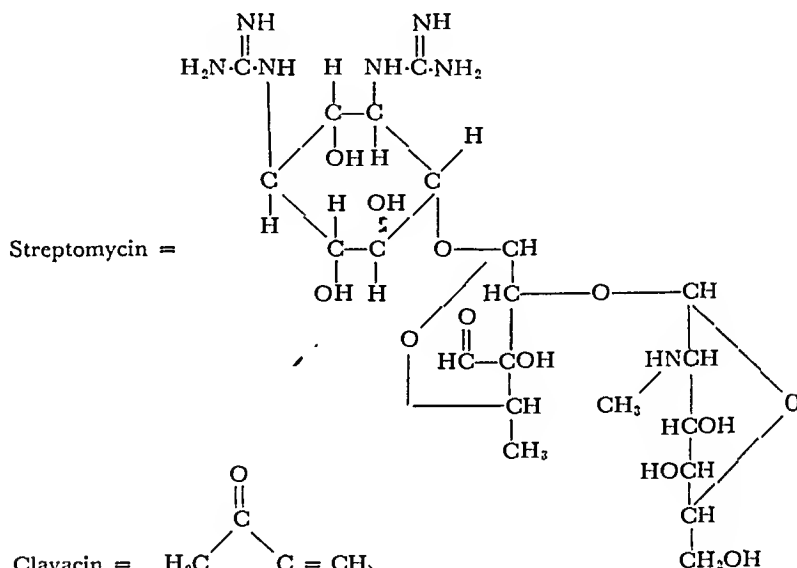
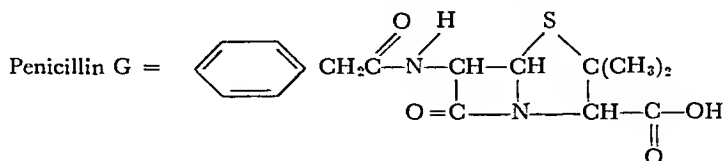
solvents and insoluble in water; it is active against a large number of bacteria and fungi. It is highly toxic.

Chetomin. Chetomin is produced by *Chaetomium cochliodes*, largely in its mycelium. It is soluble in a number of organic solvents but not in water or petroleum ether. It is

active only against certain gram-positive bacteria. It is not toxic but it is not active *in vivo*.

Penicillic acid. Penicillic acid is, like clavacin, a fairly simple compound. It is soluble in water and in organic solvents. It is produced by a variety of fungi. It is

CHEMICAL STRUCTURE OF SOME TYPICAL ANTIBIOTICS



active against a number of gram-positive and gram-negative bacteria.

Ustin. Ustin is a chlorine-containing antibiotic ($C_{19}H_{15}O_5Cl_3$). It is an acidic substance soluble in ether. It inhibits various gram-positive and acid-fast bacteria.

ANTIBIOTICS OF ACTINOMYCETES

Among the various groups of micro-organisms which are now being extensively investigated as potential producers of antibiotics, the actinomycetes occupy a prominent place. Many thousands of cultures, largely members of the genus *Streptomyces*, are being isolated and tested in numerous laboratories throughout the world. This is due to the ease with which these cultures can be obtained from soils, manures, peats, river mud, dust and other natural substrates; to the large proportion of cultures (10 to 50 per cent) that can be shown by simple methods of testing to possess antibacterial properties; and to the great practical potentialities of some of the antibiotics produced by these organisms, as shown to be the case for streptomycin.

Among the more promising antibiotics the following may be listed:

Streptomycin. Streptomycin is produced primarily by certain strains of *Streptomyces griseus*. It is isolated from the culture by adsorption on charcoal and removal with acid alcohol. It is soluble in water and insoluble in organic solvents. It is heat-stable and resistant to attack by micro-organisms. It is active against various gram-positive and gram-negative bacteria and against acid-fast bacteria, but not fungi. It is not very toxic and is used extensively in the treatment of numerous infections caused by gram-negative and penicillin-resistant gram-positive bacteria as well as upon tuberculosis. It allows ready development of resistance among sensitive bacteria.

Streptothricin. Streptothricin is produced by certain strains of *S. lavendulae*. It possesses similar properties to streptomycin but it is more toxic to animals. It is not active against various bacteria sensitive to strepto-

mycin (*B. mycoides*, *B. cereus*, *S. marcescens*) and it is active against fungi.

Chloromycetin. Chloromycetin contains organic chlorine in its molecule. It is produced by *S. venezuelae*. It is insoluble in water but soluble in organic solvents. It is active against various bacteria, against rickettsiae and against the larger viruses.

Aureomycin. Aureomycin is produced by *S. aureofaciens*. It is water-soluble, not very toxic, active against various gram-positive and gram-negative bacteria and rickettsiae; it can be administered by mouth. It is not very stable, especially in the presence of certain organic compounds.

Neomycin. Neomycin is produced by an organism closely related to *S. fradiae*. It is water-soluble and stable. It is active against various bacteria, including mycobacteria and streptomycin-resistant organisms. It is not active against fungi.

Actidione and Streptocin. These antibiotics, produced by various strains of *S. griseus*, are soluble in organic solvents. The first is primarily active against yeasts and fungi, the second is active against gram-positive bacteria and certain trichomonads.

PRODUCTION OF ANTIBIOTIC-LIKE SUBSTANCES BY PLANTS (PHYTONCIDES)

Various green plants were found to produce chemical compounds which have antibacterial properties similar to those of typical antibiotics. Some of these have been isolated and studied in detail. It is sufficient to mention allicin, a colorless oil, produced by *Allium sativum*; cassic acid produced by *Cassia reticulata*; crepin produced by *Crepis taraxacifolia*; pinosylvin produced by *Pinus sylvestris*; protoanemonin produced by *Anemone pulsatilla* and tomatin produced by the common tomato plant. They vary greatly in chemical composition; some are simple compounds, containing C, H and O; others also contain N or S. They vary in their activity upon micro-organisms and in their toxicity to animals. Certain lichens, such as spanish moss, also produce antibiotic-like materials, some of which, like usnic acid, are highly active upon the tubercle bacilli.

So far none of these plant products has found wide application in chemotherapy. It is of interest to mention the fact that quinine, a plant product, still represents an outstanding agent for the control of an important human infection, malaria.

PRODUCTION OF ANTIBIOTIC-LIKE SUBSTANCES BY ANIMALS

Animals also produce a number of substances which are characterized by antimicrobial properties similar to those of true antibiotics. One need only mention lysozyme, found in saliva, in eggs, in tears and in various mammalian tissues; erythrin, found in red blood cells; lactenin, present in milk and active upon lactic-acid bacteria; certain excreta of worms and certain protozoa.

Lysozyme, perhaps the best known of the animal products, is a polypeptide and brings about the lysis of a variety of bacteria, notably micrococci. It is water-soluble and is precipitated by various organic compounds.

None of these antibiotics have found practical application. Their role of protective mechanisms of animals against bacterial infections is still to be established.

ANTIBIOTICS AND DISEASE CONTROL

Only very few antibiotics have found practical application in the treatment of generalized or special bacterial infections or infections caused by other micro-organisms. The most important chemotherapeutic agents are the penicillins and streptomycin. Tyrothricin is used in the treatment of localized infections. Bacitracin, polymixin, aureomycin and chloromycetin appear to offer definite promise either as supplements or as independent chemotherapeutic agents. Penicillin, tyrothricin and bacitracin are active largely against gram-positive bacteria, whereas streptomycin, aureomycin and polymixin are active against both gram-positive and gram-negative bacteria as well as against acid-fast bacteria. Aureomycin and chloromycetin are active against rickettsiae and some of the larger viruses. Strepto-

thricin is active against fungi. Penicillin is highly effective against spirochaetes. Although similar in certain respects, these antibiotics possess distinct and characteristic antimicrobial spectra; they differ in chemical composition, in their mode of action on disease-producing and other bacteria and in their effects upon the cells and tissues of the host.

On the basis of available clinical information, utilization of antibiotics in the treatment of various infectious diseases can be summarized as follows, the diseases being grouped in several distinct categories:

Diseases Caused by Gram-positive Bacteria and Certain Gram-negative Cocci. The organisms causing these diseases are among the most sensitive to various antibiotics. The penicillins have found extensive application in treatment of these diseases. Bacitracin has the capacity of attacking some of these infections in a highly efficient manner. The tyrothricin complex has found application in treating wound infections. Bacteria made resistant to penicillin or strains naturally resistant to this antibiotic may still be sensitive to some of the other antibiotics, notably, bacitracin and streptomycin.

Diseases Caused by Gram-negative Bacteria. These bacteria, for the most part, are resistant to penicillin and to bacitracin but they are sensitive to several other antibiotics. One of these, streptomycin, has already found extensive application in the treatment of diseases caused by these organisms. Polymixin and aureomycin are other promising agents. The possibility of utilizing the synergistic action of two antibiotics, or of an antibiotic such as streptomycin with a synthetic agent such as sulfadiazine, offers promise of meeting the danger of rapid development of resistance of some of the bacteria to streptomycin; this has been done successfully in the treatment of certain forms of brucellosis and in certain other infections.

Diseases Caused by Mycobacteria. Because of their peculiar characteristics, diseases caused by acid-fast bacteria have proved to be among the most resistant to chemo-

therapy. *M. tuberculosis*, despite its high sensitivity to many antibiotics *in vitro*, can be attacked in the body only in a manner which involves selective tissue penetration and selective interference with the metabolism of these bacteria. The discovery that streptomycin can be utilized in the treatment of tuberculosis has provided a great stimulus in the search for new antibiotics that possess similar properties. This has given hope that the control of this highly important group of diseases is finally within our reach. The fact that streptomycin is not alone in this respect is indicated by the latent potentialities of a number of other antibiotics, such as neomycin, aureomycin, streptothricin, subtilin, nisin, clitocybin and pyolipic acid. The possible development of strains of *M. tuberculosis* resistant to streptomycin suggested the supplementary use of a synergistic agent, such as promin or other sulfones and para-aminosalicylic acid.

Spirochaetal Diseases. Several antibiotics, notably penicillin, have a remarkable effect upon diseases caused by spirochaetes. Use of penicillin in treatment of these infections gradually appears to be superseding the methods of treatment current before the advent of antibiotic therapy.

Rickettsial Diseases. A number of antibiotics are highly effective upon rickettsiae. The discovery of chloromycetin and aureomycin promises the final solution of the successful treatment of these diseases. Although no agent has yet been discovered which can be used successfully against such important diseases as the common cold or similar viruses, some of the larger viruses, such as psittacosis, lymphogranuloma and virus pneumonia, are sensitive to several antibiotics.

Fungus Diseases. A number of antibiotics, namely, hemipyocyanin, gliotoxin, clavacin, streptothricin, actidione and antimycin, are known to possess marked fungistatic and fungicidal properties. Undoubtedly one or more of these will in time find application in the control of some of the diseases caused by fungi, including both animal and plant diseases

Other Diseases. There are a large number of other infections, such as those caused by foreign cells, namely, tumors, for which no effective antibiotic is known at present. Although certain bacteria, fungi (*A. fumigatus*) and protozoa are known to be capable of attacking tumors, no successful chemotherapeutic agents have so far been found among the antibiotics.

Protozoan Diseases. Various protozoa capable of causing human infections are also subject to attack by antibiotics, as in the action of streptocin upon trichomonads, the therapeutic significance of which is still to be established.

Antibiotics have also found extensive application in the treatment of various animal diseases and of certain plant diseases.

MODE OF ACTION OF ANTIBIOTICS AND DEVELOPMENT OF RESISTANCE

The antimicrobial action of antibiotics is said to be primarily growth-inhibiting in nature, by interfering with cell growth and cell multiplication; the cell is thus made unable to grow and divide and it gradually dies. Antibiotics also possess marked bactericidal properties. The nature of the antibiotic, age of the bacterial cell, composition of the medium in which the organism grows, environmental factors of growth, all influence the effect of a given antibiotic upon bacteria. Most of the theories proposed to explain the mechanism of bacteriostatic and bactericidal activities of antibiotics are largely speculative in nature, due to insufficient experimental evidence submitted for their substantiation. Among these theories the following deserve consideration:

1. Antibiotics interfere with some of the metabolic processes of the bacterial cell by substituting for one of its essential nutrients. Substances that are structurally related to the normal cell nutrients may thus exert a specific inhibitory effect. These substances are taken up by the cell and cause blocking of the natural processes of growth. They also may interfere with utilization of the intermediary metabolic products. Streptomycin has been found, for example, to have

penicillin, its biochemical reactions were lost, the cells becoming pleomorphic and gram-negative. When the organism was made resistant to streptomycin, its characteristic biochemical reactions were also suppressed but there was no noticeable change in its morphology.

Various explanations have been suggested for the development of resistance. These may be summarized as follows: (1) Sensitive cells in a given bacterial population are killed thereby enabling the more resistant cells to grow selectively. (2) More resistant mutants are formed in a sensitive population of bacteria. (3) Acquisition of new enzyme systems or new metabolic activities permit the organism to survive in spite of the presence of the particular growth-inhibiting agent. Demerec reported that resistance of *S. aureus* to penicillin originates through a mutation mechanism and that the antibiotic acts as a selective agent to eliminate the non-resistant members of the bacterial population; the degree of resistance can be increased by selection, this increase being more rapid with each selection step.

In the development of resistance by bacteria to streptomycin, bacteria were found to produce two types of variants: One appears in small numbers in all concentrations of the antibiotic; it gives rise to cultures which grow both in streptomycin-free and in streptomycin-containing media, its virulence for animals being similar to that of the original strain. The second appears in greatest numbers in concentrations of strep-

tomycin between 100 and 400 $\mu\text{g}/\text{ml}$.; this type becomes dependent upon the presence of streptomycin in the medium; it does not grow in media containing less than 5 $\mu\text{g}/\text{ml}$. streptomycin and it is non-virulent unless the animal receives streptomycin.

Various cultures of bacteria are thus found to produce both "resistant" and "dependent" variants. The critical concentrations of streptomycin above which the sensitive strains do not grow are about the same as those below which the dependent variants do not grow. These results tend to confirm the concept that antibacterial agents act as metabolite antagonists, streptomycin interfering with some essential metabolite or metabolic process of the sensitive strains and serving as a metabolite or growth factor for the dependent strain. This relation can be reversible for the dependent strains, but it is permanent in the case of the resistant strains.

REFERENCES

1. BENEDICT, R. G. and LANGLYKKE, A. F. Antibiotics. *Ann. Rev. Microbiol.*, 1: 193-236, 1947.
2. KAVANAGH, F. Antibacterial substances from fungi and green plants. *Adv. Enzymol.*, 7: 461-511, 1947.
3. KAVANAGH, F. Activities of twenty-two antibacterial substances against nine species of bacteria. *J. Bact.*, 54: 761-766, 1947.
4. WAKSMAN, S. A. Microbial Antagonisms and Antibiotic Substances. 2nd ed., pp. 415. New York, 1948. Commonwealth Fund.
5. WAKSMAN, S. A. The Literature on Streptomycin, 1944-1948. Pp. 112. New Brunswick, 1948. Rutgers University Press.
6. WAKSMAN, S. A. Antibiotics. *Biol. Rev. Cambridge Philosop. Soc.*, 23: 452-487, 1948.

Combined Staff Clinics

The Adrenal Cortex

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University and The Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. ROBERT F. LOEB: Today we are going to review briefly the functions of the adrenal cortex as represented by two disorders which occur in man. In one of these, Addison's disease, we deal with hypofunction; in the other, Cushing's syndrome, we observe certain manifestations of hyperfunction.

Before embarking on the subject of the clinic, however, I should like to say a few words concerning the role of the endocrine glands in general. The activities of these structures, as demonstrated either by extirpation or by exhibition of their active principles, are quite extraordinary but it should not be forgotten that they play a role secondary to the intrinsic functions of the body cells. Life may go on in the absence of any one of the endocrine structures. Thus, total hypophysectomy is compatible with existence. Removal of the parathyroids does not lead to death, provided a source of calcium is made available. Total ablation of the thyroid does not result in death. Total destruction of the islands of Langerhans is compatible with existence; and indeed if accompanied by hypophysectomy or adrenalectomy, the diabetes is ameliorated. Total removal of the adrenal glands is compatible with existence if a proper external environment is provided for the tissues by maintenance of an adequate circulation through the administration of salt and water. Castration, of course, is compatible with maintenance of life. In other words, the organism as a whole can carry on the functions of oxidation, growth and cell division without any endocrine system. Perhaps it is best to consider the

endocrine glands as structures which are extraordinarily useful in meeting the exigencies of a complex society of cells; their function primarily is not to initiate the fundamental processes of metabolism but to expedite them, particularly under conditions of stress.

We might now turn directly to the subject of the discussion. I am going to outline for you some of the milestones in the history of the development of our knowledge in this field. The first observation of importance concerning the adrenal glands was made by Thomas Addison in 1849, and in 1855 he published his memorable monograph on "The Constitutional and Local Effects of Diseases of the Suprarenal Capsules" in which he pointed out that total destruction of these structures leads to death. The next year Brown-Séquard established the fact that bilateral ablation of the adrenal glands in animals resulted in death in the course of a few days. Perhaps the next important step was Abel's isolation of epinephrine from the adrenal medulla. It soon turned out that after ablation of the adrenal glands epinephrine *per se* would not maintain life; therefore, the essential vital functions apparently lay within the cells of the cortex. In 1909 Porges demonstrated the development of hypoglycemia in animals as well as in man following either extirpation or destruction of the adrenal glands. In 1916 E. K. Marshall first suggested that there might be a relation between the adrenal cortex and the kidney, because he observed that nitrogen retention and decrease in urine excretion followed bilateral adrenalectomy. Of course, this

was not evidence of a direct relationship but merely indicated the presence of severe shock with associated disturbances in renal function.

Around 1930 three groups of investigators prepared the first extracts of the adrenal

tients with Addisonian crises. It was shown also that this fall in serum sodium, as well as the abnormal elevation of serum potassium and urea nitrogen, could be alleviated by administration of sodium chloride and restoration of the serum

TABLE 1

SOME CLINICAL AND LABORATORY CHARACTERISTICS OF ADRENAL CORTICAL ACTIVITY

Hypoadrenalism

Hyperadrenalism (Cushing's Syndrome)

Electrolyte and water metabolism

Weakness, nausea, vomiting, hypotension, dehydration, reduced blood volume, shock and death; sodium loss accompanied by chloride or bicarbonate loss, potassium retention, nitrogen retention, decreased ammonia excretion

Frequent high sodium and low potassium
Hypertension

Carbohydrate and protein metabolism

Weakness, C.N.S. symptoms, hypoglycemia, increased susceptibility to stress (alarm reaction); insulin sensitivity; ? decreased glycogenesis; ? increased carbohydrate utilization; decrease in urinary corticoids and 17-ketosteroids

Diabetes mellitus, insulin resistance, skeletal demineralization, capillary fragility, "plethoric appearance," changes in body form and skin, weakness; increase in urinary corticoids, occasional increase in 17-ketosteroids

Pigmentation

? Electrolyte relationship

Sex function

Not significantly disturbed

Amenorrhea

Immunity

Lymphoid hyperplasia
Relation to protein metabolism

Depression of eosinophiles
Lymphoid hypoplasia

Nervous system instability

Mecholyl sensitivity and vagal death

Emotional instability

cortex which had some measure of physiologic activity. These groups were headed by Swingle and Pfiffner, Rogoff and Hartman. The next important advance was in isolation of the active adrenal cortical steroids and, as you know, there have been three outstanding contributors to this field, Reichstein in Switzerland and E. C. Kendall and Wintersteiner in this country. After these studies had been made progress became more rapid and the significant advances in our knowledge have become too numerous recently for detailed discussion at this time.

It was first demonstrated in this hospital in 1932 that there is a decrease in sodium concentration in the blood plasma in pa-

sodium concentration. The clinical manifestations of weakness, nausea, vomiting, arterial hypotension and collapse could be initiated by withdrawal of salt from the diet and could be dispelled by the administration of salt and water even without cortical extract. Finally, it was shown that the water and electrolyte changes, at least in part, resulted from an increased loss of sodium and water with retention of potassium by the kidney. Accumulating evidence supports this view that the electrolyte disturbances result primarily from a loss of control of renal tubular epithelium normally exerted by the adrenal cortex.

The importance of loss of salt is demonstrable by the fact that, as indicated before,

life will go on for long periods of time in the absence of the adrenal glands in the dog, rat, indeed in man when adequate salt and water are provided. Harrop and also Allers kept totally adrenalectomized dogs alive six months by forced feeding of sodium chloride and the administration of water.

Loss of sodium from the body is accompanied by a loss of chloride or bicarbonate, or both. Also, as sodium, chloride and bicarbonate are lost from the blood and interstitial fluid, and in the absence of a corresponding loss of potassium, Muntwyler and also Darrow showed that there is a shift of water to the cells, presumably to compensate for a potential osmotic disturbance. There is another change perhaps to be classified as an electrolyte disturbance, a decrease in ammonia excretion. It is not wholly established yet whether this decrease is due primarily to a failure of elaboration of ammonia in the kidney in acute adrenal insufficiency or whether it is in some way related perhaps to anoxic changes of the kidney from decreased blood flow.

Turning now to the known adrenal cortical steroids and their physiologic effects, approximately thirty different steroids, all containing the so-called cyclopentanoperhydrophenanthrene nucleus, have been isolated from the adrenals. (Fig. 1.) They may be classified chemically as follows: (1) Steroids of the C_{21} pregnane group, containing 21 carbon atoms of which 17 comprise the cyclopentanoperhydrophenanthrene nucleus, 2 represent methyl groups attached to C-10 and C-13 respectively, and 2 represent the side chain at C-17. These have either 2,3,4 or 5 oxygen atoms and include 17-hydroxycorticosterone (Compound F), 17-hydroxy-11-dehydrocorticosterone (Compound E), 11-dehydrocorticosterone (Compound A), corticosterone, desoxycorticosterone and progesterone. (2) The C_{19} androstane group, containing 19 carbon atoms (no side chain at C-17). These include androstane-11-diol-17-one and androstosterone. (3) Phenols-estrone.

The relation between the structure of the different steroids and their physiologic

activity is of interest. The steroids isolated from the adrenals may be classified in this respect as follows: (1) Steroids which affect salt and water metabolism; (2) steroids which affect carbohydrate and protein metabolism; (3) steroids which are definitely androgenic; (4) steroids which are definitely estrogenic; (5) steroids which are progestational in their activity and (6) the inactive steroids, those which as far as we know have no physiologic activity at all.

Desoxycorticosterone is distinguished by its striking effects on salt and water metabolism. The steroids with an oxygen at C-11, on the other hand, have significant effects on carbohydrate and protein metabolism (Fig. 1); those 11-oxysteroids possessing in addition an hydroxy group at C-17 have an even more striking effect, particularly 11-dehydro-17-hydroxycorticosterone, known as Compound E of Kendall. About equal in potency is 17-hydroxycorticosterone (Kendall Compound F). Next down the scale of activity is corticosterone, which has an hydroxy group on C-11 but no C-17 hydroxy group. Still less active is 11-dehydrocorticosterone (Kendall Compound A) which still has some carbohydrate and protein effects readily demonstrable in small animals and also (in the experience of Drs. Thorn, Perera, Kepler and others) slight salt and water effects in man. Desoxycorticosterone, which has neither an oxygen at C-11 nor an hydroxy group at C-17 has, as I said, an insignificant effect on carbohydrate and protein metabolism but exhibits striking effects on the reabsorption of sodium by the renal tubules and augmentation of potassium excretion.

I have asked Dr. Knowlton to talk to us at greater length on the subject of the participation of the adrenals in carbohydrate and protein metabolism.

DR. ABBIE I. KNOWLTON: Dr. Loeb has told you that as long ago as 1909 Porges reported the occurrence of hypoglycemia in adrenalectomized animals. Although this observation was made forty years ago, the influence of the adrenals upon carbohydrate metabolism is still under investigation.

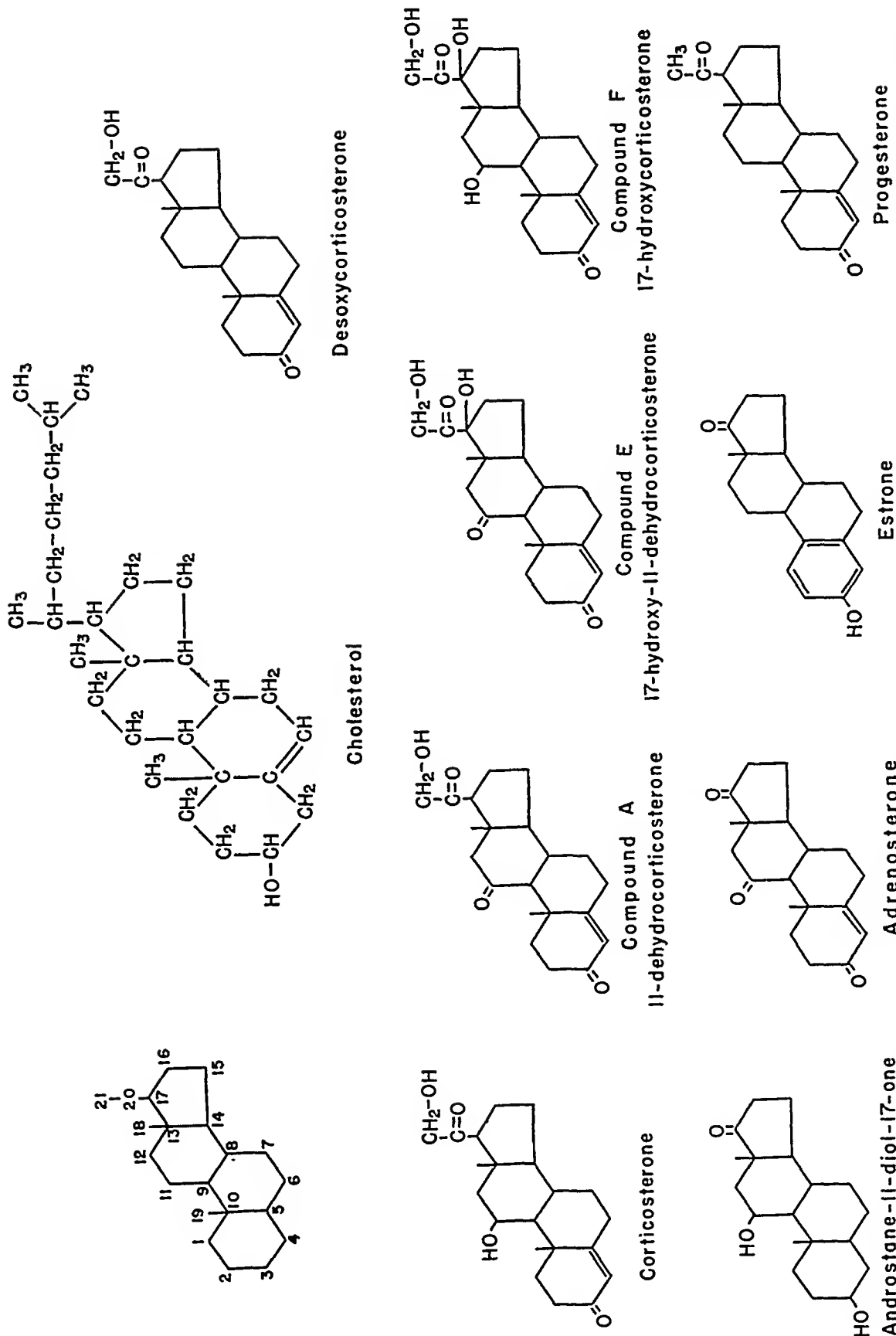


Fig. 1. Structural formulas of some adrenal cortical steroids. Upper left, the cyclopentanoperhydrophenanthrene nucleus, indicating the numbering of the carbon atoms, with substituent bonds to indicate the positions of C-18, C-19, C-20 and C-21. To the right, the full structural formula of cholesterol which the adrenal cortex can synthesize. Upper right, desoxycorticosterone, a C₂₁ compound with the pregnane grouping (in this and all subsequent formulas the methyl groups on C-10 and C-13 are indicated only by a bond). Second row: Four C₂₁ compounds with the pregnane grouping in which an oxygen is present in the C-11 position (C-11 oxysteroids). Third row: Androstane-11-diol-17-one and adrenosterone are C₁₉ compounds with the etiocholan grouping. Estrone is a C₁₈ phenol. Progesterone is a C₂₁ compound with the pregnane grouping.

The problem has presented considerable difficulty largely because many changes ensue following adrenalectomy, particularly those resulting from abnormal electrolyte balance, which may indirectly affect carbohydrate and protein metabolism. To separate these "non-specific" changes from those which may be termed "specific" has required careful study. It has required, further, studies on experimentally adrenalectomized animals in which the electrolyte disturbances have been corrected. Fortunately, at least in the rat, mouse and dog, this can be achieved by the liberal use of sodium chloride without resort to adrenal hormone substitution therapy. Ingle has emphasized the importance of such studies and in a recent review¹ gave the following three examples in which "non-specific" changes may reflect upon carbohydrate and protein metabolism.

First of all, the animal without its adrenals, unless treated, eats less than the normal animal. This may follow in large part from changes in electrolyte balance which result in dehydration, nausea and frequently vomiting. Secondly, these changes may affect absorption. In studies on the absorption of carbohydrate from the intestinal lumen, Wilbrandt and Lengyel working in Verzar's laboratory originally claimed that the adrenal cortex had an accelerating effect upon the phosphorylating processes in the gut. They demonstrated a markedly reduced rate of glucose absorption from the gut in adrenalectomized animals. However, subsequent workers have shown that if the animal is maintained on adequate amounts of sodium chloride and water, absorption of sugar proceeds at a quite normal rate. Thirdly, in 1940 Long, Katzin and Fry² pointed out that hypoglycemia and reduction in liver glycogen content did not occur in adrenalectomized rats and mice if the

animals were given access to food and salt, and that it is only under the stress of fasting that these abnormalities developed.

So much for the "non-specific" changes in carbohydrate metabolism seen after adrenalectomy. Let us consider now the evidences for a more specific action of the adrenal cortex upon these phases of metabolism. It was Long and Lukens who first demonstrated in 1934 that the insulin requirement of a diabetic dog was much reduced following adrenalectomy. Six years later Long et al.² showed in similar experiments upon diabetic rats that adrenalectomy resulted in a disappearance in glycosuria although once the animals continued to gain weight this could not be attributed to non-specific effects resulting from altered food intake or electrolyte imbalance. In addition they reported that the administration of adrenal cortical extracts led to a reappearance of urine sugar. These investigators and Wells and Kendall performed similar studies using single cortical steroids and, as Dr. Loeb has told you, found that the C₂₁ steroids which possess an oxygen atom in the 11 position (Fig. 1) all exhibit an effect upon carbohydrate metabolism. Of these Compound E of Kendall appears to be the most active and with daily injections of this steroid Ingle in 1941 reported the induction of glycosuria in normal force-fed rats. In diabetic Addisonians Thorn and Clinton³ and Sprague and Keppler⁴ both found that the use of Compound E resulted in increased glycosuria; however, in non-diabetic patients with Addison's disease Sprague et al.⁵ and Perera et al.⁶ have found disappoint-

¹ INGLE, D. J. and CLINTON, M., JR. Metabolic changes in a patient with Addison's disease following the onset of diabetes. *J. Clin. Endocrinol.*, 3: 335, 1943.

² SPRAGUE, R. G., KEPLER, E. J., KEATING, F. R., JR. and POWER, M. H. Coexisting Addison's disease and diabetes mellitus: comparative effects of Compound E (17-hydroxy-11-dehydrocorticosterone) and allied substances in 3 cases. *J. Clin. Investigation*, 26: 1198, 1947.

³ SPRAGUE, R. G., GASTINEAU, C. F., MASON, H. L. and POWER, M. H. Effects of synthetic 11-dehydrocorticosterone (Compound A) in a subject with Addison's disease. *Am. J. Med.*, 4: 175, 1948.

⁴ PERERA, G. A., PINES, K. L., HAMILTON, H. B. and VISLOCKY, K. *Am. J. Med.*, 7: 56, 1949.

¹ INGLE, D. J. The Physiological Action of the Adrenal Hormones. The Chemistry and Physiology of Hormones. Pp. 83-103, 211-243. Washington, D. C., 1944. The American Association for the Advancement of Science.

² LONG, C. N. H., KATZIN, B. and FRY, E. G. The adrenal cortex and carbohydrate metabolism. *Endocrinology*, 26: 309, 1940.

ingly little evidence of an alteration in carbohydrate metabolism. This may be said also for the use of whole adrenal extracts which in adrenal insufficiency in man produce no quantitatively significant effect upon fasting blood sugar or glucose tolerance curves. Since such extracts have an unequivocal effect in small animals, this lack of effect in the human may be a matter of dosage.

Within the last two years further evidence of the influence of the adrenals upon carbohydrate metabolism has been obtained with the use of the adrenal stimulating hormone of the pituitary—adrenocorticotrophic hormone (ACTH). In studies on normal humans receiving this substance, Mason et al.⁷ reported increased insulin resistance, Forsham et al.⁸ demonstrated some impairment of glucose tolerance, and Conn, Louis and Wheeler⁹ and also McAlphine et al.¹⁰ observed a heavy glycosuria.

As to the source of the increased carbohydrate which was observed following the injection of adrenal cortical extracts, Long et al. postulated that this was derived by gluconeogenesis from protein catabolism. However, these authors also observed that a decreased proportion of glucose was being oxidized and this now is considered the more important action. Ingle has shown that the glycosuria which occurs during the administration of Compound E is far in excess of the amount which would be expected were it derived from the breakdown of protein. Similarly, in humans receiving ACTH Conn

has observed significant glycosuria in the absence of a negative nitrogen balance. To explain such observations Ingle has postulated that the adrenal cortical hormones decrease carbohydrate utilization. An argument in favor of decreased utilization is the extraordinary resistance of Compound E-treated rats to insulin (up to 1,000 units without control of glycosuria). Similarly, Conn has reported the administration of 100 units of insulin to a normal patient receiving ACTH without control of the hormone-induced glycosuria. These findings are in accord, too, with the work of Cori¹¹ who has shown, *in vitro*, that adrenal cortical extract in the presence of anterior pituitary extract has an inhibitory effect on the initial step of glucose utilization, i.e., the conversion of glucose to glucose-6-phosphate, the step which involves the enzyme hexokinase. Insulin in this *in vitro* system acts to release the inhibition produced by these hormones.

As to the effect of the adrenals upon protein metabolism, I have already mentioned Long's contention that the C-11 oxysteroids increase the breakdown of protein and its conversion to carbohydrate. Dougherty and his group have shown that following injections of adrenocorticotrophic extracts a marked dissolution of certain body proteins, i.e., lymphoid tissue occurs. More recently Forsham et al. have pointed out a striking fall in circulating eosinophiles following the injection of adrenal hormones of the C-11 oxysteroid group or of ACTH.

Studies of these hormones have shown that they cause inhibition of growth in immature animals and may actually cause a loss of weight in adult animals. This could in part be considered the result of reciprocal action of these hormones on the pituitary gland causing depression of activity. However, Marx, Simpson and Evans in 1943 reported that ACTH counteracted the effects of growth hormone in hypophysectomized rats.

¹¹ CORI, C. F. Enzymatic reactions in carbohydrate metabolism. Harvey Lectures. Series XLI, p. 253, 1945-46.

⁷ MASON, H. L., POWER, M. H., RYNEARSON, E. A., CIARAMELLI, L. C., LI, C. H. and EVANS, H. M. Results of administration of anterior pituitary adrenocorticotrophic hormone to a normal human subject. *J. Clin. Endocrinol.*, 8: 1, 1948.

⁸ FORSHAM, P. H., THORN, G. W., PRUNTY, F. T. G. and HILLS, A. G. Clinical studies with pituitary adrenocorticotropin. *J. Clin. Endocrinol.*, 8: 15, 1948.

⁹ CONN, J. W., LOUIS, L. H. and WHEELER, C. E. Production of temporary diabetes mellitus in man with pituitary adrenocorticotrophic hormone; relation to uric acid metabolism. *J. Lab. & Clin. Med.*, 33: 651, 1948.

¹⁰ MCALPINE, H. T., VENNING, E. H., JOHNSON, L., SCHENKER, V., HOFFMAN, M. M. and BROWNE, J. S. L. Metabolic changes following the administration of pituitary adrenocorticotrophic hormone (ACTH) to normal humans. *J. Clin. Endocrinol.*, 8: 591, 1948.

It cannot be said that the adrenal cortex is essential for protein breakdown or for its conversion to sugar. Wells and Kendall in 1940 reported that phlorhizinized adrenalectomized rats fed casein were able to metabolize this protein and excrete amounts of glucose and nitrogen quite comparable to those excreted by similarly treated rats with intact adrenals. This is a further argument against the view that the adrenals have a major action on deamination of protein or on its conversion to glucose. More recently Ingle and Oberle have reported that following adrenalectomy rats excrete nitrogen in amounts comparable to sham-operated control animals.

We might return now to the clinical symptoms of hypo- and hyperadrenalism listed in Table 1. From what has been said, we might expect hypoglycemia to occur in patients with Addison's disease, especially after periods of decreased food intake. Approximately one-third of the patients studied in this hospital have symptoms referable to hypoglycemia while the majority will have occasional blood sugars below 70 mg. per cent. Frequent feedings or, in crises, liberal parenteral glucose remains the chief method of combating this disturbance since little effect upon this phase of metabolism has been demonstrated with either whole adrenal extracts or single steroids in humans. In Cushing's disease, on the other hand, decreased carbohydrate tolerance is the rule and frequently frank diabetes exists. In these patients assays of the urine for material having "corticoid" activity have been made and, as might be expected, increased amounts are present, the reverse being true in Addison's disease. Albright has postulated that the observed osteoporosis in Cushing's disease results from an abnormality in protein metabolism. Perhaps the increased bruising tendency may fit here, too. The change in body form, the "moon facies" and increased neck and

upper thorax obesity may be related to the observation of Li et al.¹² that animals receiving ACTH show an increased deposition of fat in place of protein.

In recapitulation, I think we can say that the adrenals, by virtue of their elaboration of C-11 oxysteroids, do have demonstrable effects on both carbohydrate and protein metabolism. However, I think the point which Dr. Loeb mentioned at the beginning, that the hormones do not initiate but simply facilitate or otherwise alter existing body reactions, must be remembered. The adrenalectomized animal can metabolize carbohydrate normally provided it is kept on an adequate salt intake and not subjected to stress. Likewise, protein turnover can proceed in the absence of the adrenals, as witness the growth of adrenalectomized rats maintained on sodium chloride and the elaboration of antibodies in the absence of adrenal glands (indicating anabolism) and, on the other hand, the quite normal nitrogen excretion reported by Ingle following adrenalectomy (indicating catabolism).

DR. LOEB: In addition to the steroids which are concerned with salt retention and carbohydrate and protein metabolism, some are related very closely to sex hormones and these will be discussed by Dr. Jailer.

DR. JOSEPH W. JAILER: As Dr. Loeb indicated, about thirty different steroids have been isolated from the adrenal cortex so that while the adrenal cortex may not be the seat of the soul it is certainly the stockpile of the steroids. A number of these show estrogenic or androgenic activity. Of the 17-ketosteroids excreted by normal individuals, approximately 60 per cent are of adrenal origin. However we do not know what role they play in the normal individual. It has been shown that adrenalectomized animals maintained on desoxycorticosterone or salt and water may show perfectly normal estrus cycles and if maintained in good condition conceive and go through pregnancy. In fact, it has been shown that in some species it is easier

¹² Li, C. H., SIMPSON, M. E. and EVANS, H. M. Influence of growth and adrenocorticotrophic hormones on the body composition of hypophysectomized rats. *Endocrinology*, 44: 71, 1949.

to maintain a pregnant adrenalectomized animal than an adrenalectomized animal which is not pregnant. When the animal becomes sick, the estrus cycles cease and the animal shows evidence of either estrogen or androgen withdrawal. In the female Addisonian patient menstrual periods occur normally so long as the patient remains generally well. In fact, we have in our records at the Presbyterian Hospital six pregnancies in patients with Addison's disease.

In the so-called Cushing syndrome the bulk of the adrenal steroids excreted in the urine are of the 11-oxygenated corticosteroid group. Occasionally, however, there may be increased excretion of the 17-ketosteroids, which have been isolated by several workers. Mason and Keppler at the Mayo Foundation have shown that although no physiologic manifestations of hyperandrogenism develop, androgens are found in the urine. It is in another adrenal syndrome, the so-called adrenogenital syndrome, however, that a marked increase in the excretion of 17-ketosteroids occurs. We can quote two examples from our own cases. There were two patients at the Babies Hospital quite recently, one child of six and one-half years and the other about seven years, ages in which approximately 2 mg. or so of 17-ketosteroids ordinarily are excreted daily; one excreted 175 mg. and the other 189 mg. of 17-ketosteroids. Both had adrenal tumors verified at operation.

DR. LOEB: I think it important to emphasize that adrenal cortical extract as prepared from adrenal glands does not give rise in animals to manifestations of the adrenogenital syndrome but when given in excess will produce many manifestations that one encounters in Cushing's syndrome. Thus we have some evidence to indicate that many of the manifestations of Cushing's syndrome of adrenal origin result from excessive elaboration of normal steroids whereas, as Dr. Jailer has intimated, the steroids which are elaborated in patients with the adrenogenital syndrome are, per-

haps, either qualitatively or quantitatively different. We know that abnormal steroids are excreted in the urine of some patients, in others the "target" organ is perhaps more sensitive to normal steroids with estrogenic or androgenic activity. This is a very inadequate discussion of the subject but we cannot cover the entire field in the time allotted.

STUDENT: What are corticoids?

DR. JAILER: The term "corticoids" refers to substances of undefined chemical structure (some doubtless steroids) which are present in the urine and exhibit biologic activity similar to that of certain cortical steroids. They are capable of increasing glycogen storage in young adrenalectomized rats and are protective upon exposure to cold, in the manner of adrenal cortical extract. Increased amounts of corticoids appear in the urine of subjects exposed to various kinds of stress and in the urine of patients with Cushing's syndrome.

STUDENT: Would you comment on the effects of Compound E and ACTH in rheumatoid arthritis and acute rheumatic fever?

DR. LOEB: Nothing now known about the metabolic effects of these substances would account for the striking temporary remissions they produce in rheumatoid arthritis and rheumatic fever. This is, for the present, a completely obscure phase of the role of the adrenal glands.

We now come to another uncertain chapter, namely, that concerning pigmentation. Pigmentation frequently is a prominent feature in the Addisonian patient, but there are a certain number of patients with total destruction of the adrenal glands who never develop pigmentation. It has been my impression that those who never develop pigmentation are the red-haired individuals who, perhaps, have not the cells in their skin which are capable of elaborating pigment normally. Dr. Cross might comment on this.

DR. RICHARD J. CROSS: The chief work in this field has been done by Ralli and her co-workers who became interested in reports of changes in pigmentation of

animals following adrenalectomy. They proceeded to study this phenomenon in pantothenic acid-deficient rats. As you know, the hair of black or brown rats kept on diets deficient in this vitamin turns gray and grows very poorly. It was found that if such rats had their adrenals removed a luxuriant growth of pigmented hair occurred even though the deficient diet was continued. This phenomenon was further investigated by chemical analyses of the pelts of these rats for the various substances known to play a part in melanin formation but so far it has not been possible either to localize the block present in the pantothenic acid-deficient rat or determine how adrenalectomy removes this block. It was found that if the adrenalectomized rats were maintained on desoxycorticosterone, the return of pigmentation did not occur. The same was true to a lesser extent when adrenal cortical extract was administered.

It is tempting to conclude from this that there is a reciprocal relationship between pantothenic acid and desoxycorticosterone as far as melanin formation is concerned. However, the problem is more complicated than this and at present the exact nature of the connection between adrenal cortical function and pigment metabolism, and to the pigmentation of Addison's disease is still not known.

DR. LOEB: While it is possible to keep the adrenalectomized animal alive by maintaining an adequate circulation, the adrenalectomized dog maintained on salt and water can hardly be described as a "fighting cock," and in times of stress the animal is wholly incapable of meeting physiologic demands. As you know, the relation of stress to adrenal cortical activity has been given considerable prominence in recent years through the studies of Weil and Browne, who demonstrated so-called corticoids in the urine following stress; and particularly by Selye in Montreal who introduced the concept of alarm reaction and adaptation syndrome in relation to adrenal cortical activity. I am going to ask Dr. Perera to summarize briefly the

so-called alarm reaction and adaptation phenomena as visualized by Selye.

DR. GEORGE A. PERERA: The adrenal cortex has long been known to have certain emergency functions. These are not only related to carbohydrate metabolism and hypoglycemia and, as Ingle has shown, to the capacity to perform muscular work but many investigators have commented on the vulnerability of adrenalectomized animals to many forms of stress, i.e., cold, anoxia, hemorrhage, burns and sensitivity to certain drugs such as morphine and histamine. Weil and Browne noted that following acute infections or after operative procedures, materials were excreted in the urine which prolonged the survival of adrenalectomized rats exposed to cold. It has also been observed that after stress of many types increased corticoid materials are excreted which augment the storage of glycogen in the fasted adrenalectomized animal.

The term homeostasis has been given to many reactions of adjustment to environmental change; others applied different designations to these phenomena; and Selye summarized the response to stress under the "alarm" reaction. He defined this pattern as the "sum of all of the biological phenomena elicited by sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted."

Selye found, as others had previously described in part, that many changes took place when the individual or the animal was exposed to stress. First a shock phase appeared during which the following were among the alterations noted: tachycardia, decreased muscle tone, decreased body temperature, ulcer formation in the gastrointestinal tract, hemoconcentration, anuria, edema, decreased blood chlorides, acidosis, a rise in blood sugar followed by a fall, leukopenia and then leukocytosis, increased liberation of epinephrine, decrease in blood clotting time, in fact, almost every organ and system appeared to be involved. This reaction was followed by a countershock phase, during which period there developed

enlargement of the adrenal cortex and evidence of increased activity of its cells. In addition, there was an acute involution of the thymus, of lymph nodes and of the pancreas. Degranulation of the hypophysis was observed, and during the countershock phase a reversal of most of the signs and symptoms took place that had appeared during the shock phase. Following shock and countershock a stage of resistance was described and then, if the stress was severe or prolonged, a final stage of exhaustion.

As an outgrowth of these observations Selye formulated the concept of a "general adaptation syndrome" which he defined as the "sum of all non-specific systemic reactions of the body which ensue upon long continued exposure to stress." He found, for example, that removal of the hypophysis or the cortex of the adrenals exaggerated the shock phase and rendered the countershock phase negligible or even absent. He showed in various animal species that stress of many types or the administration of large doses of desoxycorticosterone together with salt could produce an assortment of diseases and disorders. Under these conditions hypertension might develop. Lesions appeared which were similar to nephrosclerosis, periarteritis nodosa, acute rheumatic fever and rheumatoid arthritis.

From these results Selye postulated a group of disorders which he termed "diseases of adaptation" and suggested that they may arise even in man, due to inability of the organism to adjust properly to stress. Because of the fact that these disorders could not be produced after hypophysectomy or adrenalectomy, he developed a scheme to the effect that alarm produces certain catabolic impulses; these in turn affect the hypophysis and the adrenal cortex through the adrenocorticotrophic hormone; the adrenals modify carbohydrate metabolism, perhaps also the action of the thymus and lymphatic system and hence the production of antibodies; finally, such disorders as hypertension are produced by the effect of hormones of the adrenal cortex through a

cycle involving the kidneys and renin production.

No one can deny that alarm or stress in almost any species causes a major sequence of events involving practically every system, organ and tissue of the body. On the other hand, we must regard the concept of these "diseases of adaptation" as interesting but highly speculative. Attempts to reproduce some of the disturbances described by Selye, perhaps under conditions that were not quite identical, have not given comparable results. It has been pointed out that epinephrine is a potent stimulus to the adrenal cortex as demonstrated by the fact that there is a decrease in the ascorbic acid and cholesterol content of the adrenal cortical cells. An increase in corticoids in the adrenal veins was observed by Vogt. It now seems probable, as stated by Long and Sayers, that the action of epinephrine on the adrenal cortex is governed through its effect on the hypophysis.

In conclusion, we must accept the "alarm reaction" and the resultant phenomena produced; we must admit that in some way the hypophysis and the adrenal cortex may be concerned in this reaction; but we are still obliged to hold reservations regarding the concept of "diseases of adaptation." There is abundant evidence indicating that the adrenal cortex, although concerned in the "alarm reaction," may not be essential for all of the signs and symptoms which follow stress.

DR. LOEB: It is undeniable that the adrenal cortex plays a very active part in responses to stress. This is demonstrated first by the fact that the adrenalectomized animal is unable to withstand stress, and second by the fact that many forms of stress are associated with rapid depletion of the ascorbic acid content of the adrenal cortex, an important component of the adrenal cortex, and also with rapid depletion of the cholesterol content of the adrenal cortex which presumably is related somehow to synthesis of physiologically active steroids in the body. I think Dr. Perera and some of the rest of us have misgivings concerning

the concepts of Selye in that we believe that structure and functions other than those referable to the adrenal cortex may be involved in response to stress such as cold, burns, surgical operation, infections, etc. Also, the evidence which Selye offers for adrenal overactivity as the cause of rheumatic fever, appendicitis, tonsillitis and other disorders is not wholly convincing.

The next aspect of adrenal cortical function which will be discussed is one which has aroused considerable interest and is of considerable importance, namely, that of the role of the adrenal cortex in infection and resistance to infection. At the outset, I should like on purely clinical grounds to state that I do not subscribe to the thesis often propounded that patients with Addison's disease are more prone to infection than are patients with intact adrenal glands. This idea of increased susceptibility probably arises from a fact which I think is incontrovertible, namely, that the patient with Addison's disease or the adrenalectomized animal is much less in a position to cope with severe infection than is the patient or animal with adrenal glands intact, but that is a far cry from saying that susceptibility to infection is greater in the absence of the adrenals. Dr. Eisen is going to summarize for us briefly his views concerning the relationship of the adrenal cortex to antibody production and release.

DR. HERMAN N. EISEN: The idea that adrenal cortical steroids regulate the production and distribution of antibodies is based upon two beliefs: (1) that lymphocytes actually produce antibodies and gamma globulin or at least constitute a significant reservoir for these proteins, and (2) that lymphocytes readily undergo lysis upon exposure to excessive amounts of adrenal cortical steroids, thereby contributing their antibody and gamma globulin content to the blood plasma.

The evidence in support of an adrenal cortical influence on fixed and circulating lymphocytes is well established: The administration of adrenal cortical steroids or of adrenocorticotrophic hormone (ACTH)

causes a pronounced lymphopenia in blood and striking fragmentation of tissue lymphocytes with reduction in the size of lymph nodes and thymus. Furthermore, in animals and in man adrenal insufficiency is characterized by blood lymphocytosis and by a relative increase in weight of lymph nodes and thymus. The latter effects, incidentally, are commonly but mistakenly referred to as lymphoid and thymus hyperplasia. As has been shown by Dr. Herbert Stoerk, the increase in weight of the thymus in animals deprived of their adrenals is merely an approximation of the weight attained by this tissue in normal animals living under optimal conditions, i. e., in adrenalectomized animals involution of lymphoid tissue is reduced to a minimum but no true hyperplasia exists. It is interesting to note in this connection that a similar reduction in involution of lymphoid tissue (i.e., relative "hyperplasia") occurs in gonadectomized animals whose adrenals are intact, indicating that perhaps gonadal steroids also have an effect on lymphocyte dissolution.

In contradistinction to the foregoing facts, the evidence in support of the belief that lymphocytes actually form or accumulate antibodies remains controversial. It has been suspected for fifty years and perhaps longer that lymph nodes have something to do with the formation of antibodies. Few if any clear-cut experiments were done, however, until about ten years ago when McMaster and Hudaek performed the following experiment: The ears of mice were injected several times intradermally, the left ear receiving antigen A and the right ear receiving antigen B. Eight days after the last injection the serum had anti-A and anti-B agglutinins; extracts of those cervical lymph nodes which drained the left ear had relatively large amounts of anti-A but very little anti-B agglutinins, whereas similar extracts of those cervical lymph nodes which drained the right ear had relatively large amounts of anti-B but very little anti-A agglutinins. Amputation of the ears two hours after inoculation with antigen did not alter the results. This experiment

indicates that the regional lymph nodes which drain a skin site that has been injected with antigen probably forms antibody. However, as McMaster and Hudack pointed out, their results do not indicate that lymph nodes are the exclusive or even the chief site of antibody formation. And, what is more relevant to this discussion, their results do not indicate which of the several types of cells in the lymph node is responsible for antibody production. Sabin's evidence suggests that this process may be localized in the large phagocytic macrophages. More recently a number of Scandinavian workers have focused attention upon plasma cells as a possible site of antibody formation. But from the viewpoint of adrenal cortical participation the possible role of the lymphocyte is most significant since it is specifically these cells that are shattered so conspicuously by adrenal cortical steroids.

Harris and Ehrlich in an extensive series of experiments found that following the injection of antigen into the hind foot pad of rabbits the popliteal lymph nodes draining this area became enlarged and exhibited considerable lymphocyte hyperplasia. These investigators then separated lymphocytes from the lymph in the efferent lymphatic emerging from these nodes and found that extracts of these lymphocytes had antibody titers which were about seven times greater than that of the lymph from which they had been separated. It was concluded that the lymphocytes actually formed antibody. The conclusion reached was dependent upon the validity of the quantitative differences observed between lymphocytes and lymph. Despite the considerable care exercised in these experiments it has not yet been shown experimentally that the technics used are sufficiently sensitive and accurate to validate the conclusions drawn.

As you are all aware, Dougherty and White have recently attempted to demonstrate a relationship between adrenal cortical steroids, lymphocytes and antibodies. These workers immunized animals, allowed them to rest until serum antibody titers were

very low or no longer detectable, then administered ACE or ACTH, or substances which provoke increased adrenal cortical activity, and in each instance observed, concomitantly with fragmentation or lymphocytes, sharp rises in the serum antibody titers. However, a number of more recent efforts to extend these results have not confirmed the fact that massive lysis of lymphocytes in immunized animals leads to augmentation of serum antibody concentrations. In addition, a number of reports in the literature, as well as our own experiments, indicate that adrenalectomized rats and rabbits have, after immunization, serum antibody levels that are about the same as those of intact control animals similarly immunized. Indeed in some of the older reports, as well as in a recent publication by Murphy and Sturm, adrenalectomized animals are recorded as having antibody levels that are higher than those of controls but, since the possibility of hemoconcentration in the adrenalectomized animals had not been considered, such reports of elevated titers cannot be accepted. In other experiments, a group of us have found identical serum antibody and γ -globulin concentrations in (1) adrenalectomized rats which were maintained on DCA and NaCl but, lacking other cortical steroids, had as a consequence the anticipated large amount of intact lymphoid tissue and in (2) similar rats (i.e., adrenalectomized animals maintained on DCA and NaCl) given ACE and having as a result considerably reduced amounts of lymphoid tissue. These results seemed to indicate that extensive lymphocyte dissolution, induced by ACE, did not measurably contribute to serum antibody and gamma globulin levels. The possibility that such a contribution might actually have occurred but was obscured because ACE simultaneously enhanced the rate of antibody and gamma globulin degradation, along with the catabolism of other proteins, was considered but rejected after it was found that ACE had no measurable effect in adrenalectomized rats on the turnover of serum

proteins as determined through the use of heavy nitrogen (N^{15}).

Since massive lymphocyte dissolution induced by ricin, ACTH, ACE, etc., does not measurably elevate serum antibody levels, it appears that lymphocytes are not a significant reservoir for antibodies. Furthermore, the experiments reviewed indicate that the adrenal steroids do not exert a major influence upon the production or the distribution of antibody. These negative results, however, do not exclude the possibility that lymphocytes may contain a small amount of antibody which, under special circumstances that have not yet been defined, may be liberated to produce detectable augmentation of serum antibody concentration. Such a possibility would be compatible with the negative evidence accumulated above if the antibody content of lymphocytes were small relative to the total body antibody content. However, in this event the influence of the adrenal cortex on antibodies would nevertheless remain of quite minor significance.

STUDENT: Dr. Loeb, would you summarize the principles to be followed in the management of Addison's disease?

DR. LOEB: Treatment should be directed toward correcting, as far as possible, the metabolic defects present. The disturbances resulting from defects in water and electrolyte metabolism are relatively easily controlled. The disturbances in carbohydrate and protein metabolism are less amenable to therapy. The effects of stress resulting from surgical procedures and infection are still less satisfactorily controlled with the result that a number of patients continue to succumb rather suddenly even when defects in electrolyte and carbohydrate metabolism are not apparent.

A number of patients with documented Addison's disease live and work and maintain relatively good health for many years on a regimen of 10 to 20 Gm. of sodium chloride daily in addition to the salt in their diet. The majority require small doses of desoxycorticosterone in addition to a liberal salt intake. In view of the fact that this

steroid in therapeutic dosage is believed to exert an effect only on electrolyte metabolism, it is of more than passing interest that most patients treated with DCA are able to carry on a relatively normal existence and exhibit only occasional hypoglycemic episodes. In patients with recurrent symptoms of hypoglycemia little is to be gained by the daily injection of cortical extract. Indeed, even the 11-oxysteroid Compound A of Kendall in doses of 60 mg. daily has an inappreciable effect on blood sugar in these patients. Furthermore, Compound E of Kendall, which has a striking effect on glycogen storage in the rat and which intensifies diabetes in the human, in doses of 80 mg. daily has only a slight effect on the blood sugar of the Addisonian. The most satisfactory control of hypoglycemia in these patients is achieved by frequent feedings during the day and a feeding at bedtime.

In the treatment of acute crises, infusions of saline and glucose supplemented with desoxycorticosterone usually re-establish adrenal compensation. In the presence of fever or surgical intervention we have gained the clinical impression that the injection of 5 cc. of hog adrenal "lipo-extract" every eight hours and transfusion are effective adjuvants to the other measures mentioned.

SUMMARY

DR. FREDERICK K. HEATH: While the endocrine glands are not essential to living processes, they do coordinate these in the complex organism and so render it more adaptable to stress. Without an endocrine system the organism can survive often only under special conditions.

About one hundred years ago Addison first reported death following total destruction of the adrenal glands but the importance of the cortical tissue was not emphasized until almost fifty years later and then by the failure of epinephrine to support life in the total absence of the whole glands. Now, with some thirty different cortical steroids isolated, it is possible in

part to correlate cortical functions with specific chemical structure.

Substances having effects upon salt and water exchange, and carbohydrate and protein metabolism are found in the pregnane group of steroids with 21 carbon atoms. The androgenic substances fall into the class with no side chain at C-17 and therefore belong to the etiocholan group with 19 carbon atoms. Estrogenic materials are found in the phenols with 18 carbon atoms.

Control of the electrolyte balance, so far best understood of the cortical functions, was in large part worked out before the active steroids were available. It is now known that desoxycorticosterone (and to a small extent 11-dehydrocorticosterone) act upon the renal tubular cells so as to promote the reabsorption of sodium and the excretion of potassium. Individuals with Cushing's syndrome may have high serum sodium and low serum potassium levels and tend toward hydremia and hypertension. The Addisonian, on the other hand, tends toward low sodium and high potassium concentrations in the serum, dehydration and hypotension; as the tubules fail to reabsorb sodium and retain potassium, there is a loss of chloride and/or bicarbonate, nitrogen retention and a fall in urinary ammonia. The administration of salt and water with or without DCA usually reverses this trend and relieves the accompanying symptoms.

Hypoglycemia occurs in the adrenalectomized animal. Conversely, the diabetic animal is relieved by adrenalectomy and is made worse by the administration of either cortical extract or the 11-oxysteroids, particularly 11-hydro-17-hydroxycorticosterone (Compound E of Kendall). Cori offers an explanation of these findings, which are associated with decreased phosphorylation of glucose, by the *in vitro* demonstration that cortical extract increases the inhibitory effect of anterior pituitary extract on hexokinase, an inhibition antagonized by insulin.

Low blood sugar, episodes of hypoglycemia and insulin sensitivity may occur

in the Addisonian patient. Yet to date, except in hypoadrenalism with diabetes or diabetes alone, no significant effects upon carbohydrate metabolism have followed the use of any adrenal cortical substance in humans. In contrast, ACTH does exert an appreciable effect in normal man. Diabetes and insulin resistance may be seen in instances of hyperadrenalism.

The effect of the adrenal cortex upon protein metabolism is obscure. The gluconeogenic effect appears to be less than that upon carbohydrate utilization. In small animals the 11-oxysteroids seem to cause inhibition of growth during the growing phase and weight loss in mature animals.

Decreased excretion of the urinary corticoids and 17-ketosteroids occurs after adrenalectomy and in Addison's disease. Increased excretion of these compounds may be found in hyperadrenalism. There is a marked increase in 17-ketosteroid excretion in the adrenogenital syndrome which may represent the formation of abnormal steroids.

In this connection the increased urinary excretion of corticosteroids of the 11-ox group following exposure of normal animals to stress, substances which serve to protect an adrenalectomized animal under similar conditions, introduces the concept of the "alarm" reaction, "general adaptation syndrome" and the "diseases of adaptation" of Selye. The opinion was expressed that these hypotheses required more verification.

The effect of adrenal cortical materials on antibodies is probably small. No question exists as to the reduction in circulatory lymphocytes, fragmentation of tissue lymphocytes and reduction in the size of lymph nodes and thymus following the exhibition of cortical substances. On the other hand, no conclusive evidence establishes the lymphocyte *per se* as an important source of antibodies. Furthermore, adrenalectomized animals appear to form antibody as well as normal controls and no changes in immunity have been noted in Addison's disease or Cushing's syndrome.

Clinico-pathologic Conference

Progressive Hepatic Disease*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. C., (No. 154252), a twenty-seven year old white single college instructor, was admitted to the surgical service of the Barnes Hospital for the first time on December 26, 1947, complaining of jaundice. The family history was of interest only in that one of her grandparents had died of diabetes. The patient stated that she had enjoyed fairly good health most of her life. She had had seasonal hay fever for many years and at the age of twenty-one had a respiratory infection with cough and fever. The illness was complicated by bilateral thrombophlebitis, and she had pain and swelling of her legs which forced her to remain in bed for five weeks. Subsequently, she had varicose veins and persistent swelling of the legs; frequently shallow ulcers developed on the inner aspect of either ankle. A year prior to entry she had a respiratory infection with cough and fever which lasted a few weeks. Otherwise, the systemic history was non-contributory.

Two months before entry the patient developed a "head cold and sore throat" which lasted approximately three weeks. Shortly thereafter her urine became dark. She developed slight nausea after meals, her sclerae were noted to be yellow and she began to have a low grade fever. She consulted her physician who found gastrointestinal roentgenograms and cholecystograms to be normal. The patient's ieterus index was 22 units.

The jaundice gradually decreased and the urine became lighter in color. One week before admission, however, the jaundice

recurred, her urine again became quite dark and the patient was advised to enter the hospital. Aside from slight abdominal discomfort which occurred occasionally after eating she was relatively free from symptoms.

At the time of entry the temperature was 37°C., pulse 68, respirations 16 and blood pressure 100/70. The patient was well developed, well nourished and in no distress. The essential findings were mild icterus of the skin and mucous membranes, many varicosities of both legs with marked bilateral edema and large areas of hyperpigmentation about both ankles.

The laboratory findings were as follows: Blood count: red cells, 4,100,000; white cells, 3,850; hemoglobin, 12.9 Gm.; differential count: eosinophiles, 12 per cent; stab forms, 3 per cent; segmented forms, 34 per cent; lymphocytes, 49 per cent; monocytes, 2 per cent. Urinalysis: albumin, trace; sugar, negative; bile, +; urobilinogen, positive in dilution of 1:64; centrifuged sediment, negative. Blood chemistry: non-protein nitrogen, 16 mg. per cent; total protein, 9 Gm. per cent; albumin, 4.3 Gm. per cent; globulin, 4.7 Gm. per cent; ieterus index, 51 units; prothrombin time, 80 per cent of normal; bromsulfalein dye retention, 40 per cent in forty-five minutes; thymol turbidity, greater than 24 units; cephalin-cholesterol flocculation test, 3 plus. van den Bergh test: direct, 1.8 mg. per cent; indirect, 1.0 mg. per cent; total, 2.8 mg. per cent.

A diagnosis of acute catarrhal jaundice was made, and the patient was discharged

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

from the hospital on December 31, 1947. She did not restrict her activities, but jaundice persisted and although she experienced no pain or other symptoms she was re-admitted to the surgical service on March 7, 1948. Her appetite had been excellent.

At that time the essential physical findings included icterus of the skin, sclerae and mucous membranes. There was a soft blowing grade I systolic murmur at the apex but no other murmurs were described. The liver edge was easily palpable 2 cm. below the costal margin and was described as sharp but not tender. The legs appeared as on the first examination. The patient was afebrile.

The laboratory data were as follows: Blood count: red cells, 3,640,000; hemoglobin, 11.1 Gm.; white cells, 5,000; differential count: essentially normal except for 6 per cent eosinophiles. Stool: guaiac, 1 plus; negative for sodium bilirubinate. Urinalysis: The routine tests were negative. Urobilinogen was not present in abnormal amount. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 16 mg. per cent; sugar, 66 mg. per cent; total protein, 8.5 Gm. per cent; albumin, 3.1 Gm. per cent; globulin, 5.4 Gm. per cent; icterus index, 76 units; thymol turbidity, 68 units; cephalin-cholesterol flocculation test, 1 plus; prothrombin time, 38 per cent of normal. van den Bergh test: direct, 4.8 mg. per cent; indirect, 2.8 mg. per cent; alkaline phosphatase, 4 Bodansky units.

Shortly after admission an exploratory laparotomy was performed. The common bile duct was isolated and found to be normal in size. The liver and spleen were each four to five times normal size, and nodules about 1 to 1½ cm. in diameter were scattered diffusely over the entire liver. They were not described further. One, however, was removed for examination, a section of which was described by the surgical pathology department as being indicative of chronic hepatitis. It was also stated that there were dense infiltration of lymphocytic cells and the changes of early Laennec's cirrhosis. Postoperatively, the patient was given a high carbohydrate, high protein,

low fat, low salt diet with vitamin B complex, vitamin K, ammonium chloride and choline chloride, and she received one whole blood transfusion. She was discharged unimproved on March 25, 1948. Her red count was 3,052,000 and her hemoglobin was 11.9 Gm.

The patient was re-admitted to the surgical service on June 20, 1948. During the interval between admissions she had continued to feel quite well and had followed the therapeutic regimen outlined for her. The jaundice had fluctuated somewhat but she believed that it was less intense than it had been.

Physical examination again revealed moderate icterus. The liver edge could be felt 2 to 4 cm. below the right costal margin on deep inspiration. Edema of the legs was still present as before.

The essential laboratory data were as follows: Blood count: red cells, 4,310,000; hemoglobin, 12.6 Gm.; total protein, 6.6 Gm. per cent; albumin, 1.9 Gm. per cent; globulin, 4.7 Gm. per cent. van den Bergh test: sodium bilirubinate, 5.8 mg. per cent; bilirubinoglobin, 4.7 mg. per cent; total bilirubin, 10.5 mg. per cent; cephalin-cholesterol flocculation test, 4 plus; prothrombin time, 20 per cent of normal; thymol turbidity, greater than 24 units.

The patient was discharged on June 23, 1948, to continue the same therapeutic measures previously outlined. After she left the hospital she felt generally well and thought that her jaundice had diminished further. The swelling of her legs, however, increased and in addition she noted puffiness about the eyes and increased protuberance of her abdomen. About two weeks before her fourth admission a very large "black and blue" spot appeared on her left thigh, and the skin over the area "blistered." Similar smaller areas appeared over the right thigh and on both lower legs. Concomitantly, she began to note persistent bleeding from the nose and gums and also from hemorrhoids. Her temperature rose to 101°F., and mild night sweats developed. Two days before admission small raised

areas appeared over the neck, chest and buttocks and there was some stiffness of the joints. Her appetite had remained good.

She re-entered the hospital on July 19, 1948, at which time her temperature was 37.4°C., pulse 80, respirations 16 and blood pressure 120/68. The patient did not appear to be uncomfortable. There was marked edema of the lower extremities extending to the pelvis but no periorbital edema was recorded. A papular violaceous eruption with lesions 2 to 4 mm. in diameter was present over the chest and back. Some of these lesions were crusted. Over the left thigh there was a large ecchymosis measuring 10 by 20 cm. Superficially the lesion was gangrenous and blistered. Other swollen ecchymoses were present over both thighs and lower legs and there were small punched out ulcers about the left ankle. Moderate icterus of the sclerae, skin and mucous membranes was present. Clotted and crusted blood appeared in both nostrils. The gums bled easily. There was a rather harsh, high pitched systolic murmur over the entire precordium best heard along the left sternal border. The abdomen was protuberant; the flanks bulged and a fluid wave was demonstrable. The liver edge was questionably felt 4 cm. below the costal margin in the right mid-clavicular line. The spleen could not be palpated. Large, soft, inflamed external hemorrhoids were present.

The laboratory findings were as follows: Blood count: red cells, 2,950,000; hemoglobin, 8.4 Gm. per cent; white cells, 7,400; differential count: eosinophiles, 6 per cent; segmented forms, 72 per cent; lymphocytes, 20 per cent; monocytes, 2 per cent. Urinalysis: albumin, trace; sugar, negative; centrifuged sediment, 20 to 30 white blood cells per high power field; bile, positive; urobilinogen, present in a dilution of 1:128. Stool: positive for stercobilin. Blood chemistry: non-protein nitrogen, 15 mg. per cent; sugar, 42 mg. per cent; total protein, 6.9 Gm. per cent; albumin, 1.8 Gm. per cent; globulin, 5.1 Gm. per cent; prothrombin time, 14 per cent of normal; van den Bergh test: direct, 3.9 mg. per cent; indirect,

3.6 mg. per cent; total, 7.5 mg. per cent; cephalin-cholesterol flocculation test, 4 plus; thymol turbidity test, 35 units; serum phosphorus, 4.9 mg. per cent; alkaline phosphatase, 6 Bodansky units. Electrocardiogram: left axis deviation. Roentgenogram of the chest: bilateral pleural effusion, small.

The patient was given increased carbohydrate in her diet and received serum albumin and intrahepatol followed by whole blood transfusions. During her first two weeks in the hospital several spontaneous ecchymoses appeared. The prothrombin time remained 15 per cent of normal. Two weeks after admission an infected hematoma on the left thigh ruptured and purulent material drained. The patient's temperature rose to 38°C., and she was given penicillin. A similar sequence of events occurred, the involved lesion being on the right thigh. One month after entry the patient's prothrombin time was 19 per cent of normal. The red cell count was 3,000,000 and her hemoglobin, 8.8 Gm. She continued to receive 10 cc. of intrahepatol three times weekly and large amounts of vitamin B complex and vitamin K parenterally. Complete liver function studies revealed that the cephalin-cholesterol flocculation test was 4 plus, thymol turbidity, 33 units; icterus index, 36 units, total protein, 6.5 Gm. per cent, albumin 1.8 Gm. per cent and globulin 4.7 Gm. per cent. The urine contained urobilinogen in a dilution of 1 to 40 and was negative for bile. A trace of bile was present in the stool. Two months after entry there was little change in either the physical condition or the laboratory findings except that the white blood cells in the urine had disappeared. At the time of discharge on October 5, 1948, the patient had lost 32 pounds. There was considerable improvement in the surgical lesions of the lower extremities and edema was diminished. Aside from the slight rise in temperature at the time of rupture of the lesions on her thighs the patient had been afebrile.

She returned home and for ten days her condition remained unchanged. Tenderness along the varicose veins of the left leg then

developed and red raised lesions appeared around the left ankle which subsequently became necrotic and drained purulent material. She began to have afternoon temperature elevation and signs of inflammation in the left thigh appeared. She had not, however, been troubled by additional abnormal bleeding. She was admitted for the last time on October 30, 1948.

Physical examination at that time revealed the temperature to be 39.5°C., the pulse 94, respirations 18 and blood pressure 100/70. The patient was lying flat in bed with her legs drawn up. Her skin was pale and sallow. The neck veins were prominent. There were a few ecchymotic spots over the thighs. Scleral icterus was slight. Edema was present in both lower extremities, particularly on the left, and a number of small ulcers surrounded the left ankle. There was a healing ulcer on the lateral aspect of the right thigh and on the anteromedial aspect of the left thigh; marked redness, tenderness and swelling were noted. The inguinal nodes were non-tender. Breath sounds were moderately impaired at the left base. A grade II, soft blowing systolic murmur was heard at the apex and the base. The liver edge was felt 4 cm. below the right costal margin in the mid-clavicular line; it was slightly tender. The spleen tip could be palpated when the patient took a deep breath.

Laboratory data were as follows: Blood count: red cells, 3,117,000; hemoglobin, 9.5 Gm.; white cell count, normal; differential: normal. Urinalysis: negative except for an occasional red blood cell in the centrifuged sediment. Stool: guaiac, 1 plus. Blood chemistry: non-protein nitrogen, 17 mg. per cent; total protein, 5.9 Gm. per cent; albumin, 2.1; globulin, 3.8 Gm. per cent; cephalin-cholesterol flocculation, 2 plus; thymol turbidity, 26 units; prothrombin time, 27 per cent of normal; icterus index, 31 units; van den Bergh test, sodium bilirubinate, 2.5 mg. per cent; bilirubinglobin, 3.4 mg. per cent; total bilirubin, 5.9 mg. per cent. Blood culture: negative.

The patient was treated symptomatically. The day after admission the abscess on the

left thigh was opened; approximately 1 pint of purulent material was withdrawn and a drain was inserted. That night she developed spontaneous ecchymoses in the right deltoid region. Following drainage of the thigh abscess, however, she felt better and her temperature decreased somewhat. Spontaneous skin hemorrhages continued to occur. On the day before death her red cell count was 2,730,000, with 9.1 Gm of hemoglobin. Her white cell count had risen to 15,050 and the differential count showed a left shift; the white cells were described as showing marked toxic granulation. The blood platelet count was 51,000. The patient received 500 cc. of fresh whole blood without reaction. On the final day of life, November 5, 1948, she complained of nausea and vomited early in the morning. The vomitus contained no blood. She was given a small amount of dilaudid for her restlessness. That afternoon she was found dead in bed. Tarry, fecal material issued from the rectum.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presents a number of interesting problems, and we shall not have time to discuss them all. We shall, however, attempt to cover the most interesting and important points. This young woman had apparently enjoyed good health until the time she developed jaundice which was essentially asymptomatic. She was admitted as a patient on the surgical service where a diagnosis of acute catarrhal jaundice was made. Dr. Wade, would you comment on that diagnosis: On the basis of the data at hand what diagnosis would you make?

DR. LEO J. WADE: The term "acute catarrhal jaundice" is misleading and should be discarded. We would rather use "acute infectious hepatitis" to characterize this disease entity.

DR. W. BARRY WOOD, JR.: I agree with Dr. Wade's comment regarding the term acute catarrhal jaundice. Probably the illness which used to be called acute catarrhal

jaundice was the same as that which we now call acute infectious hepatitis.

DR. GUSTAVE J. DAMMIN: I believe that leptospirosis of the liver has also been called acute infectious hepatitis. In my opinion we should be more definite—since this disease is viral in origin and epidemic in character, it should be called “epidemic viral hepatitis.” In that way we likewise differentiate between it and homologous serum jaundice, a disease which is also viral in origin but which is transmitted in a different way.

DR. ALEXANDER: Viral epidemic hepatitis and homologous serum jaundice are similar in their clinical pictures although there are certain significant differences in the two. The question as to whether they are one disease or two diseases has now been clarified and I shall ask Dr. Harford to compare these two syndromes.

DR. CARL G. HARFORD: The two viruses are closely related but there are, as you have pointed out, Dr. Alexander, significant differences. For example, the virus of homologous serum jaundice, or serum hepatitis as it is sometimes called, is not found in feces and it is not transmissible by ingestion of fecal filtrates. In contrast, viral epidemic hepatitis may be transmitted by ingestion of fecal filtrates and the virus often may be recovered from the stools of patients with the disease. Furthermore, the incubation period in homologous serum jaundice is much longer than is the case with viral epidemic hepatitis and the virus of the former may be detected in the blood very early in the incubation period; I believe, in one instance at least, the virus was isolated eighty-seven days before icterus developed. Patients who have recovered from one of the two forms of jaundice are said to be susceptible to the other. It has been extremely difficult to elucidate all the desired facts for these diseases can be produced only in human volunteers.

DR. ALEXANDER: Do you believe the causative agents are variants of the same virus or do you believe they are different viruses?

DR. HARFORD: It is my opinion that the two are very closely related, probably in much the same way as different strains of the influenza virus are related or as St. Louis encephalitis is related to equine encephalitis. It is not uncommon for two related viruses to cause very similar disease pictures in humans or animals.

DR. ALEXANDER: We should now return to the case under discussion. It will be recalled that following discharge from the hospital the patient's jaundice did not regress and two months later she returned for the second admission. Following study of the liver function, an exploratory laparotomy was performed. I should like to ask Dr. Moore whether or not liver function tests may be used in an attempt to differentiate between jaundice due to extrahepatic biliary obstruction and jaundice primarily due to hepatocellular damage.

DR. CARL V. MOORE: In a very high percentage of cases one should be able to differentiate between hepatogenous jaundice and extrahepatic obstructive jaundice on the basis of liver function studies. In this patient data are available to permit such differentiation and a diagnosis of hepatogenous jaundice can be made with reasonable certainty. For example, the cephalin-cholesterol flocculation was 3 plus on one occasion and then 1 plus. Thymol turbidity was elevated and it is particularly significant that the second determination was probably higher than the first since the first determination was recorded to be greater than 24 units. The alkaline phosphatase was only 4 Bodansky units and if one takes that finding with the others he can, with reasonable assurance, assume that there was no extrahepatic obstruction. The results of the liver function studies justified exploratory laparotomy for the purpose of obtaining a liver biopsy but such laboratory data as these do not constitute an indication for exploration of the common bile duct. I should like to call attention to the statement in the protocol, “she did not restrict her activities.” I believe it is well to point out here that there is very

little in the way of specific therapy in the treatment of hepatitis. One of the considerations in the management of such patients, which is now generally accepted, is that their activity should be greatly restricted during the active phase of the disease. It has been shown rather clearly that a return to activity before recovery occurs definitely exerts an untoward effect.

DR. ALEXANDER: I should like to ask Dr. Robert Moore to describe the histologic findings at the time of liver biopsy.

DR. ROBERT A. MOORE: The hepatic tissue was divided into lobules but the lobulation was irregular; in a number of areas connective tissue divided a given lobule. The connective tissue was loose and heavily infiltrated with lymphocytes and mononuclear cells. Some of the hepatic cells were binucleated; this observation may be interpreted as indicating that the liver had suffered injury and active regeneration of hepatic cells was taking place. The cytoplasm of the cells was reticulated as one would expect if there were reasonable storage of glycogen. All in all, there was a definite increase in fibrous tissue and marked lymphocytic infiltration. If one considers the findings objectively, he must conclude that the liver had been subject to injury over a moderately lengthy period of time, this statement being based on the definite increase in fibrous tissue. Further, it seems that the noxious stimulus was still active, as evidenced by the heavy infiltration of cells within the fibrous tissue and by the fact that the liver cells were actively dividing.

DR. ALEXANDER: Following operation the patient made an uneventful recovery and continued to feel remarkably well. Her third admission was for re-evaluation.

DR. WOOD: Had she continued to be fully active following operation?

DR. RALPH V. GIESELMAN: Yes, she had.

DR. ALEXANDER: She continued to have a good appetite and physical examination was essentially unchanged. Her laboratory findings, however, were perhaps somewhat more abnormal. The bilirubin had risen

and the cephalin-cholesterol flocculation was now 4 plus. Likewise, the thymol turbidity was increased and it reasonably would be concluded that the disease was progressing. By the time of her fourth admission, one month later, she had become quite ill. Bleeding from the gums and into the skin had occurred and in addition marked dependent edema and ascites developed. Dr. Smith, would you tell us why, in your opinion, this patient developed edema and ascites?

DR. JOHN R. SMITH: The sudden appearance of edema in a patient such as this one raises the question first of all as to whether marked portal hypertension had developed. The accumulation of ascitic fluid, perhaps largely at first on the basis of increased hydrostatic pressure within the abdomen, may lead to compression of the vena cava, elevation of the venous pressure in the legs and edema. I am not sure that the hypoalbuminemia was severe enough to explain the edema *per se*.

DR. C. V. MOORE: If one calculates the osmotic pressure on the basis of the plasma protein figures given, he finds that the results indeed are low enough to explain the occurrence of edema.

DR. ALEXANDER: The patient subsequently had episodes which suggested thromboses in the veins and in the arteries. You will remember that at the age of twenty-one following a respiratory infection she had remained in bed for five weeks because of swelling in her legs and that subsequently she had varicose veins and recurrent leg swelling. Do you believe that she had severe thrombophlebitis at that time?

DR. SMITH: I believe that she may well have had severe phlebothrombosis and as a result chronic severe obstruction developed.

DR. ALEXANDER: During her stay in the hospital the patient received intensive treatment including parenteral vitamin B complex, serum albumin, transfusions and crude liver extracts. Intrahepatol was also given. Dr. Moore, would you comment on the latter substance?

DR. C. V. MOORE: My experience with intrahepatol has been limited. We have been discouraged, however, by the severe febrile reactions in patients to whom it has been given. Dr. Shank and Dr. Charles Hoagland at the Rockefeller Institute used intrapheptol extensively; may we have Dr. Shank discuss this agent?

DR. ROBERT E. SHANK: At the Hospital of the Rockefeller Institute we treated a group of forty patients with cirrhosis with crude liver extract prepared in the laboratory there. It differed only from the crude commercial preparations in that the pH of extraction was higher and pyrogenic substances were removed by treatment with permutit. Large quantities were administered intravenously and the patients were followed for periods of from two to four years. The survival rate after two years, which was about 70 per cent, was substantially greater than that reported by Patek and others using dietary therapy alone. Intrahepatol is a commercial modification of the original preparation. The pharmaceutical house which prepares it has attempted to concentrate the product. In a limited experience it was our impression that reactions occurred somewhat more frequently than with the original extract.

DR. ALEXANDER: At the time of the patient's final admission her liver function tests seemed to have improved, particularly when compared with the results of her studies on previous admissions. Would you comment on that point, Dr. Dammin?

DR. DAMMIN: There are several instances in which cirrhosis has progressed to an extreme degree, concomitantly with the return of thymol turbidity and cephalin-cholesterol flocculation values to normal. In this case the very prolonged prothrombin time and the failure of response to vitamin K suggest severe hepatic damage. It should be pointed out that no one knows exactly what the thymol turbidity and cephalin-cholesterol flocculation tests measure. There is some evidence that they represent abnormality in the nature of protein components and that they

may not actually reflect what is happening in the liver cells *per se*.

DR. ALEXANDER: Let us attempt to establish the etiology in this case if possible. Is this history entirely compatible with epidemic viral hepatitis?

DR. SHANK: Yes, I think it is. It is not unusual for patients with this disease to have prolonged periods of low grade fever. More frequently this febrile period is brief. Most patients recover from epidemic hepatitis in a period of from four to nine weeks. The acute course, however, may be prolonged in some individuals and hepatic function may return to normal only after periods of months. In another group of cases intermittent, acute episodes occur with ultimate recovery. Finally, a small but important number of patients following an attack of epidemic hepatitis are left with residual hepatic dysfunction. Some of this group develop cirrhosis. It is impossible at this time to state the frequency with which cirrhosis occurs. Our experience has not been of sufficient duration to afford us adequate data but among some 400 patients studied at the Hospital of the Rockefeller Institute there were two deaths. One of these patients died in the acute phase of the disease. A number of other patients now have evidence of persistent hepatic dysfunction. Other investigators have found a higher incidence of cirrhosis, but there are some groups in which the incidence is indeed very low.

DR. ALEXANDER: The biopsy specimen which Dr. Moore showed us was obtained three months after the onset of jaundice and as you will recall showed marked fibrosis. Do you believe that this entire process may have occurred within these three months?

DR. SHANK: Yes, I do.

DR. ALEXANDER: Could this disease have been so-called toxic cirrhosis such as is seen in metal intoxication?

DR. SHANK: The course of that type of liver damage is usually quite acute, leading to death rather rapidly or at least to a prolonged severe course.

DR. VIRGIL C. SCOTT: When this patient first became ill, the liver was not the only organ affected. I would like to have Dr. Shank discuss this point.

DR. SHANK: It is true that the major pathologic findings in viral hepatitis are in the liver but many patients have splenomegaly and frequently there is gastrointestinal involvement such as gastroduodenitis. Often widespread lymphoid hyperplasia is demonstrable. I think it is well to consider this disease as a generalized infection with most prominent manifestations in the liver.

DR. ALEXANDER: Do you believe that the pathologists will be able to establish the diagnosis of viral epidemic hepatitis without qualification?

DR. SHANK: The morphologic findings demonstrable at autopsy in cirrhosis which follows epidemic viral hepatitis are variable and do not permit differentiation from other types of cirrhosis.

DR. SMITH: How frequently is infectious hepatitis followed by carcinoma of the liver?

DR. R. A. MOORE: I believe Dr. Shank's statement in regard to the fact that none of these patients has been followed for a sufficient time to know the ultimate effects applies to your question, too, Dr. Smith. So far as I know there are no specific studies on that point.

DR. ALEXANDER: I believe then that we are all agreed that this patient had epidemic viral hepatitis with progressive hepatic damage leading to cirrhosis and ultimately to death.

DR. WOOD: I would like to return for a moment to the question of terminology for I believe that this case illustrates very pointedly the need for discarding the term "catarrhal jaundice." Catarrhal jaundice was always thought to be an essentially benign disease which physicians tended to treat lightly. During the past war it was learned that infectious hepatitis was indeed a serious disease and this patient's course illustrates how very serious a form the disease may take. As Dr. Carl Moore has brought out so clearly this patient was treated actually as if she had "catarrhal

jaundice" whereas had she been treated as a patient with infectious hepatitis according to the regimen outlined by the Army physicians—that is prolonged bed rest until all evidence of hepatic disease had abated—she might well have avoided this fatal outcome.

Clinical Diagnosis: Viral epidemic hepatitis (acute infectious hepatitis), cirrhosis of the liver.

PATHOLOGIC DISCUSSION

DR. ANTONIO VILLASANA: External examination revealed light yellow discoloration of the sclerae. Over the right deltoid region, the right thigh and left ankle there were extensive areas of ecchymosis; the area over the thigh was covered with a number of blebs which contained sanguineous fluid. On the medial aspect of the left thigh and left ankle there were several ulcers and several pigmented scars; distinct pitting edema of the lower extremities was noted. The skeletal muscles, subcutaneous tissues and all the viscera were pale, somewhat dry and opaque. The heart, which weighed 400 Gm., was enlarged and flabby but exhibited no lesion other than fat infiltration of the myocardium.

There were 1,200 cc. of clear amber fluid in the peritoneal cavity. The liver, which was brownish-yellow in color, weighed 1,150 Gm. and was firm and rubbery in consistency. The left lobe of the liver was particularly small. The capsule was thickened and the surface was coarsely nodular; the size of the nodules varied from 0.5 to 4 cm. in diameter. Cut section revealed a striking difference between the right and the left lobes. The parenchyma in the left lobe was extensively replaced by edematous, translucent, yellowish-gray fibrous tissue. In the right lobe there were both small and large bulging nodules separated by the same yellowish-gray, translucent connective tissue. The spleen was enlarged to a weight of 400 Gm. It was soft and dark red with several areas of hemorrhage in the parenchyma. The stomach, which was dilated,

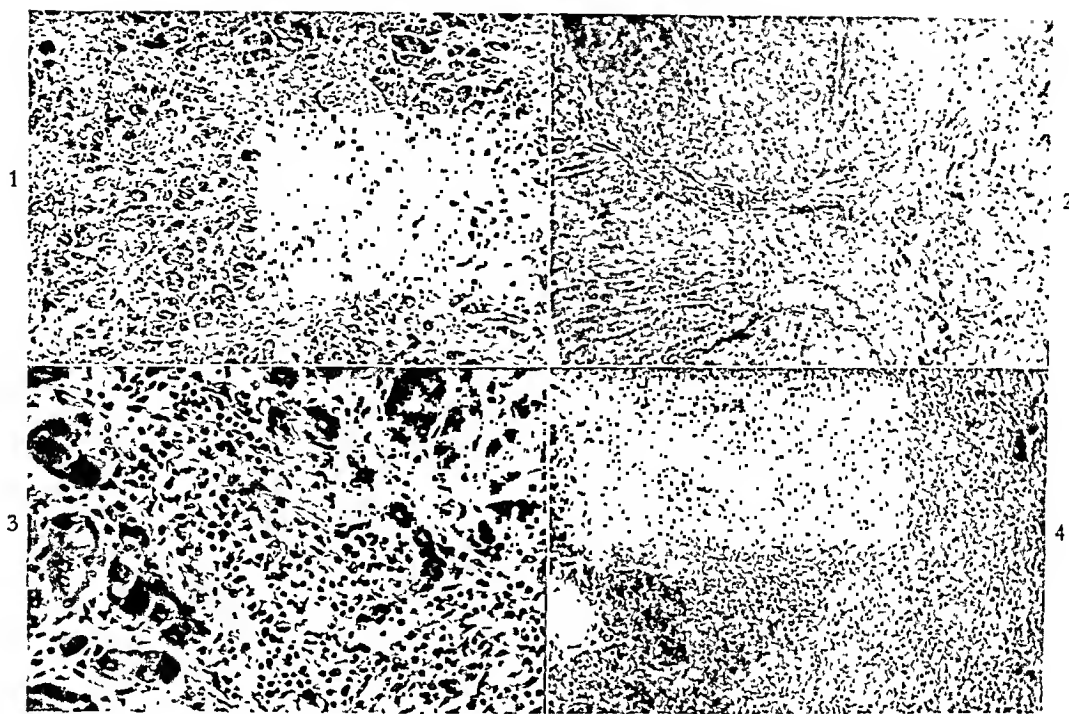


FIG. 1. A section of the left lobe of the liver composed of broad bands of connective tissue and distorted hepatic cells in small groups.

FIG. 2. Right lobe of the liver with increased periportal tissue and lobules without central veins.

FIG. 3. Details of the distorted hepatic cells with regenerative changes and cellular infiltration of the portal space.

FIG. 4. Spleen with prominent sinusoids and parenchymal hemorrhage of chronic passive congestion.

contained about 500 cc. of dark turbid fluid with food remnants and granular sediment. The gastric mucosa was smooth with few rugae and a number of petechiae. In the lumen of the large intestine there were approximately 1,000 cc. of fresh and altered blood. The mucosa was edematous, but no bleeding points could be demonstrated. In the endometrium there was a polypoid focus which on cut section revealed numerous cystic spaces filled with mucoid material. The lower peri-aortic lymph nodes were enlarged and succulent with a few petechiae in the parenchyma on cut section.

DR. R. A. MOORE: From the gross description it is apparent this case represents some type of cirrhosis of the liver; the existence of portal hypertension is suggested by the enlarged and congested spleen and the fluid in the peritoneal cavity. Presumably the terminal event can be associated with the finding of large amounts of blood in the large intestine although attempts to demonstrate a bleeding point were unsuccessful.

The first illustration (Fig. 1) was taken from the left lobe of the liver. There is diffuse fibrosis about small islands and groups of hepatic cells which show extreme multinucleation; occasionally there are actually large confluent masses of hepatic cytoplasm with multiple nuclei. The hepatic cells are not arranged in a lobular pattern and the connective tissue in between is moderately dense and mature but is infiltrated with lymphocytes and mononuclear cells to a slight or moderate degree. Contrast this picture with the next one (Fig. 2) which was taken from the right lobe of the liver. The reason for the difference in the gross appearance is immediately evident. Here there is definite lobulation; the appearance is not unlike that seen in a surgical biopsy specimen, except that at autopsy there was less activity, the connective tissue was more mature and the outline of the lobules of hepatic tissue was more distinct. Note that at the right side of the illustration there is irregular proliferation of tissue into a lobule.

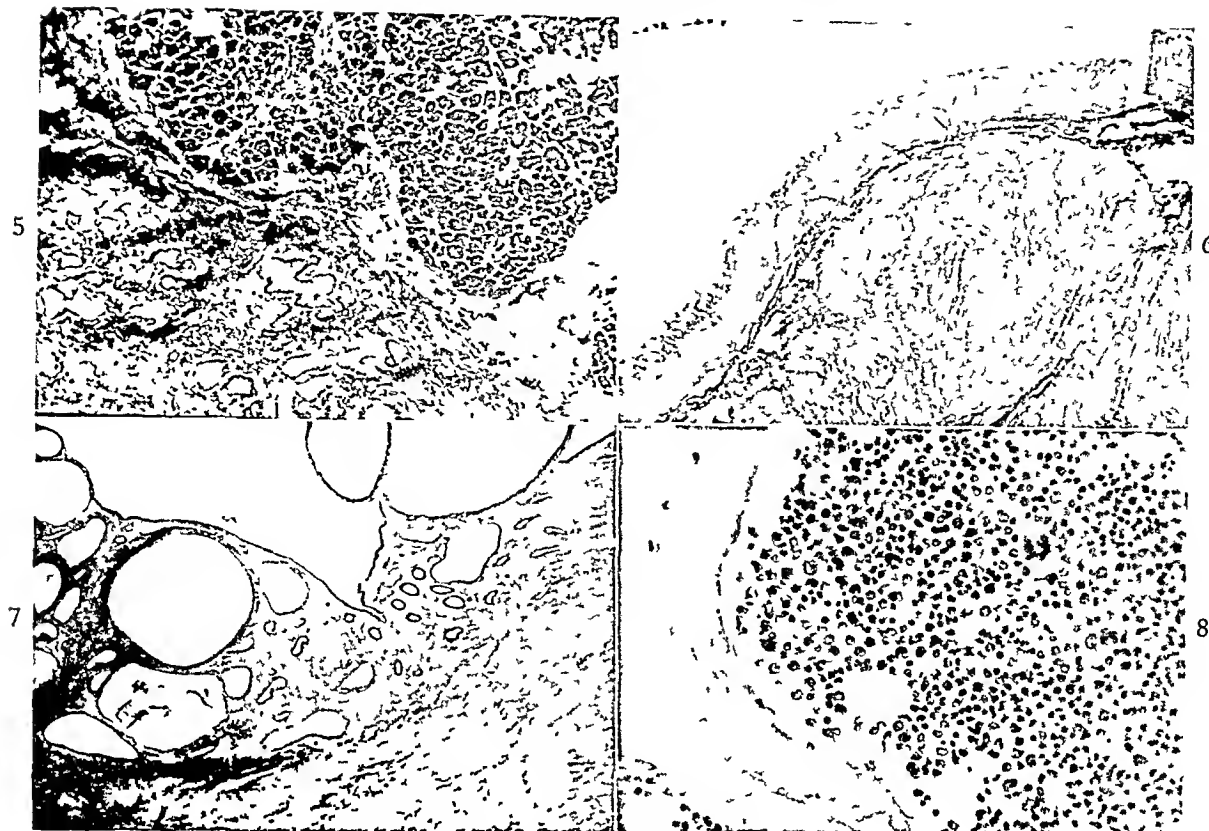


FIG. 5. Slight interstitial infiltration of lymphocytes in the pancreas.

FIG. 6. Atrophic mucosa in a section of the stomach.

FIG. 7. Endometrium with typical dilated glands of cystic hyperplasia.

FIG. 8. Moderately hyperplastic bone marrow in which there is a relative lack of the more mature erythroid forms.

The normal hepatic lobule always contains a central vein and the hepatic cells radiate in a definite cord-like pattern to the periphery. When liver regenerates, it rarely if ever regenerates in that pattern, but rather in the pattern which was noted here—the hepatic cords are not arranged in as orderly a fashion. There is a suggestion of radial arrangement but in the centers of these lobules there is no central vein. That change constitutes objective evidence that this tissue was not residual original hepatic tissue but rather regenerated hepatic tissue. The contrast in the microscopic findings in the left and right lobe of the liver represents a difference in the type and amount of regeneration. In the right lobe there had been extensive regeneration with formation of nodules while in the left lobe regeneration had not advanced to the same extent and had not taken on the lobular pattern which is so characteristic of classical cirrhosis of the liver.

Figure 3 is a section under a higher magnification from the left lobe of the liver

in which there are cells with a large amount of basophilic, globular, granular material in the cytoplasm, supposedly nucleoproteins of the cytoplasmic type associated with active regeneration; prominent nucleoli, also indicative of active regeneration, are likewise seen. Multinucleation of hepatic cells was obvious. The connective tissue was loose and infiltrated with large numbers of cells.

The next illustration (Fig. 4) is a section from the spleen. There is prominent dilatation of the sinusoids and hemorrhage into the red pulp indicative of congestion of long-standing. In a section from the pancreas (Fig. 5) there is slight interstitial fibrosis and cellular infiltration of a few lymphocytes, particularly out into the paraductal tissue. The next section (Fig. 6) is taken from the stomach and shows mucosa with the muscularis beneath it. The mucosa was definitely atrophic and thinner than normal. Atrophy involved not only the gastric mucosa but also the duodenal mucosa as well.

A section of the endometrium (Fig. 7)

shows the typical changes of cystic hyperplasia. This lesion is allegedly associated with some disturbance in estrogen metabolism; certainly a patient with as much hepatic damage as this woman might well have had sufficient disturbance in estrogen metabolism to have had endometrial stimulation.

Figure 8 is a section of the bone marrow showing diffuse hyperplasia; mature cells of the erythroid series are relatively decreased in number in comparison with less mature forms, indicating slight maturation arrest in the red cell series.

I think that pathologists have had more difficulty with cases of this type, particularly in regard to terminology, than have the clinicians; acute catarrhal jaundice, toxic cirrhosis and acute and subacute yellow atrophy perhaps all belong in the same category. I am not at all sure that enough is known to permit sharp morphologic distinction between these various types of hepatic disease, but the criteria of distinction which are in current use may be presented, and they apparently rest upon a reasonably firm foundation.

First, what type of cirrhosis was present in this case—was it Laennec's portal cirrhosis or some other form? Fifteen or twenty-five years ago there appeared in the pathologic literature descriptions of the type of cirrhosis which is called toxic cirrhosis—or from a descriptive standpoint, multilobular cirrhosis of the liver—in order to distinguish it from simple lobular cirrhosis of the Laennec type. That idea developed because of cases similar to the present one in which there were nodules throughout cut sections of the liver separated by variable amounts of connective tissue. In almost every instance, however, there was some focus in which lobulation was absent. To explain the origin of such a lesion it was logical to postulate that the liver was exposed to an extensive insult of very short duration which destroyed large areas to such a degree that regeneration had not, or could not, occur. In other regions the damage presumably was less severe and

regeneration occurred with resultant formation of nodules varying in size. Such was the accepted concept in regard to the pathogenesis of toxic cirrhosis.

During the last century acute yellow atrophy and subacute yellow atrophy were also described, the former being those cases which exhibited a fulminating course and massive destruction of tissue and the latter diagnosis being assigned to those cases which were less severe in their course and in the extent of tissue destruction. In the acute cases there was outright necrosis of the hepatic cells without proliferation of fibrous tissue and with only a minimal amount of cellular infiltration. In patients who survived for a sufficient period of time fibrous tissue proliferated, regeneration of liver cells ensued and the pathologic picture of subacute yellow atrophy developed.

In the course of time those two major concepts, namely, toxic cirrhosis and acute or subacute yellow atrophy, were combined to some extent, in that acute yellow atrophy in a few instances and toxic cirrhosis in some instances (but neither in every instance) were observed to follow the ingestion of some noxious substance. Cinchophen, arsenic and many other chemical agents were found to be hepatotoxic. It was inferred that single doses of these substances injured the liver and therefore the term toxic cirrhosis of the liver was thought applicable. I think it has become apparent in recent years that although the concept of acute yellow atrophy as a disease produced by toxic agents is still tenable, most examples of acute yellow atrophy, subacute yellow atrophy and toxic or multilobular cirrhosis of the liver represent varying stages of the disease, epidemic viral hepatitis.

I think this brief recapitulation of the history of the concept of this disease from the pathologic standpoint indicates that the pathologist is not in a position to make an outright diagnosis of epidemic viral hepatitis. He can, however, state that the pathologic changes are consistent with that diagnosis if it can be supported on a clinical basis. The same comments apply, of course,

to homologous serum jaundice as to epidemic viral hepatitis.

In the case which we are discussing today the lesions found in the liver are consistent with those one would expect to find in a patient with epidemic viral hepatitis who had recovered to the extent that regeneration of the liver without restoration of the normal structural pattern had occurred. Fortunately, in most patients who have epidemic viral hepatitis recovery is complete.

A finding which interested us a great deal was atrophy of the gastric mucosa and the slight maturation arrest in the red cells series. I gave Dr. Carl Moore a note earlier in the conference and asked him if he could tell us if that finding could be correlated with a lesion which had caused severe hepatic dysfunction.

DR. C. V. MOORE: It is known that in most patients with cirrhosis or severe hepatic insufficiency normocytic or slightly macrocytic anemia frequently develops which, however, does not respond to the anti-pernicious anemia principle in liver. Rarely, one does see a patient who has marked hepatic damage and a megaloblastic bone marrow who responds quite specifically to liver. Whether this particular patient is in that category or not I do not know, but I would doubt it. It is conceivable that the changes observed in the bone marrow and in the gastric mucosa may be explained on the basis of an antipernicious anemia factor deficiency, but I would doubt that also. Probably the bone marrow abnormality could better be related to the infection present; in this regard it is well to note that the neutrophils were deficient in granules and there were other evidences of bone marrow depression. Atrophy of the gastric mucosa probably cannot be attributed to infection.

DR. ALEXANDER: I would like to ask why Dr. Balduin Lucké stated that cirrhosis did not seem to be a sequence of epidemic hepatitis.

DR. R. A. MOORE: It is my understanding that at the time Dr. Lucké published his paper he had not seen cases such as this one. Is that not right, Dr. Dammin?

DR. DAMMIN: Yes. He later qualified his statement somewhat and said that a single bout of hepatitis does not result in cirrhosis.

DR. R. A. MOORE: Dr. Lucké's first report was based on early observations. Cirrhosis following epidemic viral hepatitis has been observed by others many times since Lucké's original paper.

It was unfortunate that in the autopsy Virchow did in 1850 on a patient who had this very disease he demonstrated mucous plugs in the ampulla of Vater and no necrosis of the liver; otherwise the whole concept of acute catarrhal jaundice would never have developed. Dr. Cecil Watson has recently demonstrated by means of multiple biopsies of the liver that there are occasions when there may be no significant microscopic changes in that organ during the disease.

DR. DAMMIN: In this case the liver function tests revealed a progression of the disease. At the time of exploration the surgeon noted that the liver was uniformly enlarged but at autopsy the left lobe was more severely scarred than the right. It is postulated that this difference occurs because the elements that protect the hepatic parenchyma are apparently drawn from the small intestine and reach the right lobe of the liver in greater concentration than the left lobe which is consequently less protected.

Anatomic Diagnoses: Cirrhosis of the liver with predominantly peripheral fibrosis and marked reduction in parenchyma; fresh and altered blood in the gastrointestinal tract (1,000 cc.); atrophy of the gastric and duodenal mucosa; hyperplasia of the vertebral marrow; cystic hyperplasia of the endometrium.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SOUTHERN SECTIONAL MEETING HELD IN NEW ORLEANS, JANUARY 28, 1949

IMMUNE RESPONSE TO H. PERTUSSIS VACCINATION. A STUDY USING THE PASSIVE INTRAPERITONEAL MOUSE PROTECTION TEST. *John P. McGovern, M.D., (introduced by Grant Taylor, M.D.), Durham, North Carolina.*

Mouse protective antibodies were assayed and compared with agglutinating antibodies following immunization with a phase 1 H. pertussis vaccine in a group of young infants. A total of thirty infants, three to six months of age with no history of or exposure to clinical whooping cough, were subjected to inoculation three times at two-week intervals with a phase 1 pertussis vaccine, each infant receiving an approximate total of 100 billion organisms. Blood samples were drawn before as well as after immunization. Sera from these blood samples were used in an attempt to protect mice passively against lethal intraperitoneal challenging doses of pertussis organisms suspended in a 4 per cent gastric hog mucin solution. Each serum was also tested for agglutinating antibodies by a rapid agglutination technic. Control groups of mice were used in each experiment.

It was found that these infants did not possess mouse protective antibodies in their serum but that these antibodies consistently develop following inoculation of the infant with sufficient phase 1 pertussis vaccine. It was shown also that agglutinating antibodies did not develop consistently nor did they parallel in degree the mouse protective values.

DIFFUSION OF STREPTOMYCIN INTO SEROUS CAVITIES FOLLOWING INTRAMUSCULAR INJECTION. *Patrick B. Storey, M.D. (by invitation), Walter Kurland, M.D. (by invitation), Helen Murphy, B.S. (by invitation), Sol Katz, M.D. (by invitation) and Harold L. Hirsh, M.D. (introduced by Jay A. Robinson, M.D.), Washington, D. C.*

From the Georgetown Medical and Tuberculosis Divisions, Gallinger Municipal Hospital, and Department of Medicine, Georgetown University School of Medicine.

Spinal fluid was obtained from thirty-eight patients with pulmonary tuberculosis without meningitis. All but two of the patients studied had had therapy for at least three weeks. The two patients were studied during the first two days of therapy in order to determine the rapidity with which streptomycin appeared in the spinal fluid. On dosage schedules of 1 Gm. every six hours streptomycin was not detected in the spinal fluid one or two hours after the first dose whereas assayable levels were found at twelve hours. Of the twenty patients who were receiving 2 to 4 Gm. per day in divided doses every six to twelve hours, all had spinal fluid concentrations of 0.15 to 0.6 micrograms per cc. Only 50 per cent of the patients receiving 1 Gm. per day had a level of 0.15 to 0.3 micrograms per cc. of spinal fluid. Two patients with tuberculous meningitis were treated with streptomycin intramuscularly, one of whom received 1 Gm. every twelve hours and the other 1 Gm. every six hours. In the first patient repeated specimens of spinal fluid were found to contain 0.3 micrograms per cc. Assay of specimens of spinal fluid from the second patient revealed no detectable levels at one hour, 2.5 micrograms per cc. at twelve hours and 5 micrograms per cc. at twenty-four and seventy-two hours after therapy was started.

Four patients with infectious arthritis and one with hydro-arthritis who were on streptomycin intramuscularly in doses of 1 and 3 Gm. per day were studied. Joint fluid levels obtained during therapy ranged from 2.5 to 5.0 micrograms per cc.

There were ten patients with acute tuberculous pleurisy with effusion who received doses of 1 to 2 Gm. of streptomycin per day. Maximum levels of 2.5 to 5.0 micrograms were found in the pleural fluid after several days of therapy.

Two patients with portal cirrhosis on dosage schedules of 1 to 2 Gm. of streptomycin per day showed from 2.5 to 5.0 micrograms per cc. of ascitic fluid. One patient with a tuberculous pericardial effusion on a 2 Gm. per day dosage schedule showed levels of 5 and 10 micrograms per cc. of pericardial fluid.

THERAPEUTIC VALUE OF SMALL DOSES OF STREPTOMYCIN IN TUBERCULOSIS. *Bernard Milloff, M.D. (by invitation), Sol Katz, M.D. and Harold L. Hirsh, M.D., (introduced by Hyman Zimmerman, M.D.), Washington, D. C.*

From the Georgetown Medical and Tuberculosis Divisions, Gallinger Municipal Hospital, and the Department of Medicine, Georgetown University School of Medicine.

A variety of tuberculous infections were treated with small doses of streptomycin. All patients received $\frac{1}{2}$ Gm. per day in one dose, except four with miliary tuberculosis who were given $\frac{1}{2}$ Gm. twice a day.

Five patients with miliary tuberculosis were treated and none survived. Four patients with bronchial tuberculosis treated for one to four months showed a definite beneficial response. Two patients with proved tuberculous pericarditis were treated. In one the response was favorable while the other developed progressive tuberculosis and died. Two patients showed clearing of the tuberculous peritonitis, however, several months after completion of therapy hematogenous tuberculosis became manifest in both. Treatment was re-instituted with no response.

Seven patients with draining sinuses showed closure of the sinuses. In two patients with tuberculous bursitis incision and drainings while under streptomycin therapy resulted in healing. In forty patients with eighty-six operations, which included thoracoplasty, lobectomy and pneumonectomy, no tuberculous spreads occurred with the use of $\frac{1}{2}$ Gm. per day in a single injection for seven days preoperatively and postoperatively.

Streptomycin in doses of $\frac{1}{2}$ Gm. per day would appear to be definitely effective in the treatment of bronchial tuberculosis and draining sinuses. It would also be recommended that this same dosage be used in the prevention of tuberculous spread in the surgery of tuberculous patients.

GROWTH ENHANCEMENT OF M. TUBERCULOSIS BY STREPTOMYCIN. *Max Michael, Jr., M.D., Martin Cummings, M.D., George Spendlove, M.D. and William B. Fackler, Jr., M.D., Atlanta, Georgia.*

From the Medical Service, Lawson VA Hospital and the Department of Medicine, Emory University School of Medicine and the Tuberculosis Evaluation Laboratory, USPHS.

The development of bacterial resistance to streptomycin is a well documented phenomenon. Of recent interest is the finding that a few strains of bacteria appear to be not only resistant to but actually dependent upon streptomycin for growth. This study is concerned with a strain of the tubercle bacillus which demonstrates enhancement of growth by streptomycin. The strain was isolated from the sputum of a patient with pulmonary tuberculosis on the ninety-sixth day of streptomycin therapy. It was the impression of the observers that the disease was actually made worse toward the end of the course of streptomycin but it is obviously difficult to draw any conclusion as to cause and effect in a disease of such clinical variability.

The organism displayed the following characteristics: When cultured in tubes containing 0, 1, 5, 10, 100 and 1,000 micrograms per ml. of streptomycin it grew luxuriantly in all tubes containing streptomycin but quite sparsely in the control tube without the antibiotic. This was observed repeatedly, both in liquid Dubos media and on solid Lowenstein media. A sample of the patient's sputum obtained three months after the termination of therapy displayed the same phenomenon.

Guinea pig experiments have suggested that the observed enhancement of growth *in vitro* also occurs *in vivo*. Animals infected with this strain and treated with streptomycin had a shorter survival time than did those which were untreated.

A FACTOR IN RABBIT POLYMORPHONUCLEAR LEUKOCYTES WHICH CAUSES A RISE IN BODY TEMPERATURE. *Paul B. Beeson, M.D., Atlanta, Georgia.*

A plausible explanation of the fevers which accompany many different kinds of disease is that some product of tissue injury affects the

function of temperature-regulating centers in the hypothalamus. The findings described here were obtained during an attempt to demonstrate such a substance. Rabbits were used as experimental animals. Various types of tissue were subjected to mechanical lysis and then tested for capacity to cause elevation of temperature in normal rabbits. The following cells or tissues have been so studied: erythrocytes, lymphocytes, macrophages, polymorphonuclear leukocytes, liver, brain, kidney, lung, spleen and muscle. Positive results were obtained only with polymorphonuclear leukocytes. These were obtained from intraperitoneal exudates produced by injection of large quantities of sterile physiologic salt solution. The cells were separated from the exudates by centrifugation, washed and then lysed by shaking with glass beads. Centrifugation of this material in a small quantity of saline yielded a clear supernatant fluid and cellular debris. The cellular debris did not provoke fever but the clear supernatant fluid was active. An extract of leukocytes obtained from the peritoneal exudate of one rabbit produced a rise of 1 to 3°F: within one hour when injected intravenously into a normal rabbit. The agent responsible for the temperature rise was not dialyzable through a collodion membrane and was inactivated by heating to 75 to 80°F. It was not precipitated at 50 per cent saturation with sodium sulfate but was precipitated at full saturation. The activity of this factor is inhibited by antipyretic drugs.

METABOLIC CHANGES ASSOCIATED WITH THE ADMINISTRATION OF SALT-POOR HUMAN SERUM ALBUMIN IN INFECTIOUS HEPATITIS. *W. Parson, M.D., H. S. Mayerson, M.D. (by invitation), W. J. Trautman, Jr., M.D. (by invitation) and R. Hutcheson, M.D. (by invitation), New Orleans, Louisiana.*

From the Departments of Physiology and Medicine, School of Medicine, Tulane University and the Alton Ochsner Medical Foundation.

Two patients suffering from infectious hepatitis were studied on a metabolic regimen for periods of thirty to thirty-five days, respectively. Large doses (75 Gm.) of salt-poor human serum albumin were administered daily during two separate six-day periods to the first patient and during one six-day period to the second patient. The latter was subsequently fed a protein

supplement during one period and the results were compared with those obtained after albumin administration. Daily nitrogen, calcium and phosphorus balances were obtained as well as frequent determinations of the plasma proteins, red cell and plasma volumes. The results indicate that administered salt-poor human serum albumin is retained almost quantitatively and can be considered as a useful source of nitrogen in situations in which marked anabolism is present.

VITAMIN B₁₂ THERAPY FOR MEGALOBlastic ANEMIA OF INFANCY. *A. Z. McPherson, M.D. and U. Jonsson, M.D. (introduced by Grant Taylor, M.D.), Durham, North Carolina.*

A severe anemia with megaloblastic blood formation in the marrow occasionally develops in infancy in association with infection and/or dietary inadequacy. The anemia responds specifically to liver extract or to pteroylglutamic acid.

Two infants with megaloblastic anemia were treated with vitamin B₁₂ with favorable results. An eleven months old colored infant had been fed only breast milk. Development was retarded. She finally became weak, irritable and acutely ill. On admission the hemoglobin was 3.2 Gm./100 cc., red blood cells 1,100,000, white blood cells 20,000, hematocrit 10 per cent, mean corpuscular volume 92 cu. micra., reticulocytes 7.4 per cent and platelets 24,000 per c.u. mm. Immature granulocytes and nucleated red blood cells were present in the circulating blood. The bone marrow showed megaloblastic cell development. A single dose of 0.002 mg. of vitamin B₁₂ was injected intramuscularly. On the seventh day a reticulocyte peak of 69.1 per cent was reached and the blood values had more than doubled. On the fourteenth day the hemoglobin was 7.8 Gm., red blood cells 2,800,000, white blood cells 13,350, hematocrit 30 per cent, mean corpuscular value 104 cu. micra. and reticulocytes 13.5 per cent. The platelets were normal in number and immature granulocytes were no longer present in the circulating blood although a few nucleated red blood cells still remained. The bone marrow was normoblastic.

A second infant, a seven months old white male, had eaten poorly for four months despite an adequate diet. Anemia was discovered before

admission and blood transfusions were given. He remained weak, ate poorly and vomited often. The hemoglobin was 10.9 Gm./100 cc., red blood cells 3,100,000, white blood cells 5,500, hematocrit 29.5 per cent, mean corpuscular value 93 cu. micra. and reticulocytes 1.3 per cent. Bone marrow examination showed megaloblastic cell development. Vitamin B₁₂ (0.002 mg.) was injected intramuscularly. The blood values continued to fall for six days. Vitamin B₁₂ (0.005 mg.) was then injected and two days later an unsustained reticulocytosis of 31.7 per cent occurred. With a daily dose of 0.002 mg. of vitamin B₁₂, there was a sustained reticulocytosis and rapid gain in blood values.

TREATMENT OF ACUTE LEUKEMIA WITH AMINOPTERIN. *Paul Maness, M.D., O. C. Hansen-Pruss, M.D., A. Z. McPherson, M.D. and Leland D. Stoddard, M.D. (introduced by Grant Taylor), Durham, North Carolina.*

Nine patients with acute leukemia, seven children ranging in age from thirteen months to fourteen years and two adults twenty-five and forty-five years old, were treated with aminopterin. In seven patients the leukemia was myeloblastic and in two it was lymphoblastic. The total dose of the drug per patient varied from 3.5 to 20 mg. Stomatitis developed in four patients. Leukocytosis in five patients decreased but there was no improvement in the hemoglobin or red cell values. Serial bone marrow examinations showed some increase in cell maturity in four cases during aminopterin therapy. A temporary remission lasting three weeks or longer occurred twice. Four patients died in the hospital after being treated from three days to five weeks. Some evidence of hematologic improvement attributable to the drug was seen in three of these patients. Three patients continue to take the drug. One child with lymphoblastic leukemia showed no observable effect from the drug and in the other there was a fall in the white cell count and symptomatic improvement after taking 20 mg. in one month.

Autopsy study in four cases showed focal areas of hemorrhage and necrosis in the bone marrow as the outstanding finding.

While aminopterin has a demonstrable hematologic effect in some patients with leukemia,

and may even produce a temporary remission, the net clinical benefit does not appear to be great enough to justify its use except in experimental therapy.

CHEMOTHERAPEUTIC ACTIVITY OF DERIVATIVES OF PTEROYL GLUTAMIC ACID AGAINST TRANSMITTED LEUKEMIA IN MICE. *J. H. Burchenal, M.D., J. R. Burchenal, M.D. and E. Robinson, M.D., New York, New York.*

From the Section on Mouse Leukemia of the Division of Experimental Chemotherapy, the Sloan-Kettering Institute for Cancer Research.

Because of the promising results reported by Farber and others from the use of 4-amino-pteroyl glutamic acid in the treatment of acute leukemia, it was believed that compounds structurally related to pteroyl glutamic acid should be screened against transmitted mouse leukemia. Leukemia Ak 4, an acute lymphoid strain in the Akm stock of mice, was used in these experiments. Most of the ninety derivatives tested to date have shown no real chemotherapeutic activity, but the four following compounds significantly prolonged the survival time of the treated animals: 4-amino-N¹⁰-methyl-pteroyl glutamic acid; 2, 6-diaminopurine; 4-amino-pteroyl aspartic acid and 4-amino-pteroyl glutamic acid.

Repeated tests of these compounds have demonstrated that 4-amino-N¹⁰-methyl-PGA and 2,6-diaminopurine consistently prolonged by from 50 to 100 per cent the survival time of mice injected with this strain of leukemia. Less work has been done to date on 4-amino-pteroyl aspartic acid but these experiments as well as others against less acute leukemias indicate that this compound has a chemotherapeutic activity approximately equal to the two just mentioned. 4-amino-pteroyl glutamic acid is the most toxic of the derivatives so far tested, but it does not show as great an effect on transmitted mouse leukemia as the other three.

It is interesting to note that these four compounds have analogous structures. The similarity lies in the substitution by amino groups in the 2 and 4 positions of the pyrimidine ring. All have also been shown to act in varying degrees as antagonists of pteroyl glutamic acid in the growth requirements of *Lactobacillus casei*.

EFFECTS OF 4-AMINO-PTEROYL GLUTAMIC ACID AND RELATED COMPOUNDS ON NEOPLASTIC DISEASE. *J. H. Burchenal, M.D., D. A. Karnofsky, M.D., W. P. L. Myers, M.D., C. M. Southam, M.D., L. F. Craver, M.D. and C. P. Rhoads, M.D., New York, New York.*

From the Section on Mouse Leukemia of the Division of Experimental Chemotherapy, the Sloan-Kettering Institute for Cancer Research.

A total of thirty-eight patients with leukemias and various forms of neoplastic disease have been treated with 4-amino-pteroyl glutamic acid at Memorial Hospital since March, 1948. Doses have varied from 1 mg. per day in children to a top dose of 4.7 mg. a day over an eight-day period for one adult. Toxic symptoms were frequent in our series. Of the thirty-one patients who received at least 0.2 mg./Kg. and were observed for at least forty-eight hours after the start of therapy twenty-six developed stomatitis, nine diarrhea, nine loss of hair and five various types of rash.

Thirteen patients with acute leukemias, seven children and six adults, were treated. Of these nine died without any significant benefit and two had temporary partial remissions lasting about five weeks and then they died despite further therapy, 107 and 185 days, respectively, after the start of treatment. Two patients are surviving with almost complete clinical and hematologic remissions. In one of these patients there have been three separate remissions following re-administration of the drug.

Nine patients with chronic myelocytic leukemia were treated. Two of them were terminal and died before receiving adequate amounts of the drug for evaluation. Of the remaining seven a fall in white blood cells occurred in all, there was improvement in the differential count in six, a rise in hemoglobin in two, a decrease in the spleen size in five and subjective improvement in six. Three patients with chronic lymphocytic leukemia were treated with no benefit and a high incidence of toxic manifestations. Five patients with Hodgkin's disease, four lymphosarcomas in adults, two carcinomas of the lung and one carcinoma of the bladder and one mycosis fungoides, showed little or no response to therapy even when the dosage was pushed to toxic levels.

BONE MARROW STUDIES IN PATIENTS TREATED WITH 4 AMINO-PTEROYLGLUTAMIC ACID, 4 AMINO N¹⁰ METHYL PTEROYL-GLUTAMIC ACID AND 4 AMINO-PTEROYL-ASPARTIC ACID. *J. B. Thiersch, M.D. (introduced by J. H. Burchenal, M.D.), New York, New York.*

Serial bone marrow examinations were conducted on twenty-one patients with tumors and leukemia who were treated with antifolic compounds. The effect of these compounds on the myeloid and erythroid series was studied and no qualitative distinction between the action of the different agents was found. The myeloid elements were markedly decreased; the eosinophiles being least affected. Giant metamyelocytes and hypersegmented polymorphonuclears appeared in abnormal numbers. The erythroid series, while decreased *in toto*, appeared to be relatively prominent compared to the myeloid series. Pathologic nuclear remnants often combined with coarse basophile stippling were found in giant erythrocytes. The orthochromatic normoblasts were decreased in numbers and sometimes absent. Basophile normoblasts and erythroblasts increased and finally atypical but definite basophile megaloblasts appeared, reaching a maximum of 52 per cent of all nucleated erythroid elements. Platelets and megacaryocytes were less affected.

An erythromegaloblastosis was produced in patients with lymphosarcoma and chronic lymphatic leukemia. This was reversed in eight days with folic acid in one case but did not remit spontaneously in twenty-nine days in one other case. No effect on the lymphoid series was observed in these patients.

Two cases of acute leukemia responded with megaloblastic changes in the erythroid series and further decrease of the mature myeloid elements. Patients with chronic myeloid leukemia gave only a moderate decrease of total cellularity and changes in the erythroid series as just described.

Two patients with lymphosarcoma with bone marrow involvement and two patients with acute leukemia showed a decrease in abnormal cells and a reversion toward normal composition.

EXTRACELLULAR WATER CONTENT OF THE HEART IN DOGS SUBJECTED TO HEMORRHAGIC SHOCK MEASURED WITH THE RADIOACTIVE ISOTOPE OF SODIUM. *Ned D.*

Rodes, M.D., Janet M. Lemley, M.D., Alice B. Dale, M.D., Sam E. Stephenson, Jr., M.D., Herbert L. Glass, M.D. and George R. Meneely, M.D., Nashville, Tennessee.

From the Departments of Biochemistry, Medicine and Surgery of Vanderbilt University School of Medicine and the Research Laboratory of Thayer Veterans Administration Hospital, Nashville, Tennessee.

The method of Manery and Bale was employed to measure the extracellular water of the myocardium in three groups of dogs. The first group was subjected to severe hemorrhagic hypotension to produce irreversible shock by the technic of Wiggers. The second group represented positive controls in that they were treated in the same manner as the shock dogs but were not bled. The third group, which served as negative controls, were given large and rapidly administered intravenous infusions of saline.

The positive control dogs showed an extracellular water content in the myocardium of 23.5 per cent of the wet weight of tissue. This is in quite close accord with the data of Manery and Balc. The negative control dogs developed an edema of the myocardium obvious on gross and microscopic examination. The extracellular water in these hearts was 46.2 per cent of the wet weight of the tissue. This is significantly and convincingly different from the positive controls. Thus the method is adequate to detect edema when it is present.

The extracellular water in the myocardium of the dogs subjected to Wiggers' hemorrhagic hypotension procedure was 24.7 per cent of the wet weight of tissue. There is, therefore, no edema of the heart in dogs subjected to this form of irreversible shock.

DETERMINATION OF PLASMA VOLUME USING HUMAN SERUM ALBUMIN TAGGED WITH RADIOACTIVE IODINE 131. *Robert Niesel, M.D. (by invitation), Blanche Porter, M.D. (by invitation), and Kenneth R. Crispell, M.D. (by invitation) (introduced by William Parson, M.D.), New Orleans, Louisiana.*

From the Biophysics Laboratory, Tulane University.

Human serum albumin was chosen as the tracer vehicle since it was desirable to develop a method applicable to humans. The tracer

chosen was I 131 since it is known to combine chemically with the amino acid, tyrosine. Human serum albumin contains approximately 4½ per cent of tyrosine. The radioactive iodine I 131, as obtained from Isotopes Division of Atomic Energy Commission, is present as an iodide. To facilitate the tagging of albumin the iodine must be available in a free state. The iodine is then combined with the albumin in an alkaline solution. The iodo-albumin mixture is dialyzed to remove all inorganic iodide compounds.

Preliminary observations were carried out on dogs. This method compares favorably with the plasma dye method in determining the plasma volume. A disadvantage of the plasma dye method is the difficulty encountered in repeated frequent determinations on the same subject. The iodo-albumin method is not subject to such limitations provided the tolerance dose of radiation is not exceeded.

Preliminary studies seem to indicate that the iodo-albumin method is applicable to human subjects. The determination of plasma volume in four patients gave values which agreed within 10 to 15 per cent with those obtained using the plasma dye method.

REGRESSION OF A RADIOACTIVE MERCURIAL DIURETIC FROM THE PLASMA OF MAN.

C. T. Ray, M.D., S. A. Threefoot, M.D., G. E. Burch, M.D., J. A. Cronvich, M.D. (by invitation), J. P. Milnor, M.D., P. B. Reaser, M.D., W. J. Overman, M.D. and W. H. Gordon, M.D., New Orleans, Louisiana.

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital and the Department of Medicine and School of Electrical Engineering.

During the study of the mechanism of chronic congestive heart failure and other edematous states investigations were carried out with the use of radioactive mercury incorporated into a mercurial diuretic (mercuhydrin) in order to observe the concentration-time course of the isotope in the plasma of man after intravenous injection. Fifteen subjects were studied. Labeled mercurial diuretic (2 cc.) were injected into the antecubital vein of one arm of the subjects, and blood samples were drawn at close intervals from the antecubital vein of the contralateral side. The serum concentration regression curves

observed in all subjects were similar. The curves were analyzed graphically into three exponential rates of regression.

The regression rates contributing to the concentration-time course of radioactive mercury in the plasma of man are not simple phenomena; rather they are probably the expression of many simultaneously occurring physicochemical processes. The most rapid regression rate is brought about largely by mechanical mixing of the tracer in the plasma along with some extremely rapidly occurring biologic events. The second regression rate probably expresses the filling of the potential mercury spaces and the activation of "potential turnover patterns" for mercury, including diffusion and chemical reactions, which did not actually exist until a relatively large quantity (78 mg.) of the element was administered. The third regression rate is most likely primarily a reflection of the elimination of the mercury from the body, principally urinary.

This analysis of the regression of mercury from the plasma of man is undoubtedly an oversimplification of multiple complex phenomena but it serves as a basis for an understanding of other data dependent upon the concentration of mercury in the plasma.

CLINICAL USE OF THE NEW MONOTHIOL MERCURIAL DIURETIC—THIOMERIN. *A. Ruskin, M.D., J. E. Johnson, M.D. and W. N. Roddy, M.D., Galveston, Texas.*

In experiments on the isolated rabbit heart we noted the cardiotoxic and cardiolethal dosages of thiomerin (Campbell) to be approximately twenty times those of mercurhydride (mercuhydrin), the diuretic in present use.

The subcutaneous administration in patients with edema of various origins, 2 cc. doses, of equal mercury content (80 mg.) in daily rotation with 2 cc. of mercuhydrin produced the following results: In twenty-four instances the twenty-four-hour weight loss was identical following either diuretic; in sixty-two patients thiomerin produced up to three times as great a weight loss; in twelve the weight loss was from four to nine times as great with thiomerin as with mercuhydrin. Mercuhydrin was followed by a greater weight loss up to three times that following thiomerin in fifty instances; in ten the weight loss was four to eight times greater.

These results indicate the near-equivalence

of diuretic effects following doses of mercuhydrin and thiomerin of equal mercury content. The maximum weight loss for either drug was 9 pounds, the maximum excess of output over the intake 7 L. Reactions following an earlier lot of thiomerin were moderate in the form of inflammatory nodules at the site of injection; only mild infrequent soreness resulted from the newer lots of the drug. Thiomerin resulted in no toxic effects on the kidneys or the electrocardiogram. It was effective and harmless when mercuhydrin produced reactions.

VARIATIONS IN THE EFFECT OF DIGITALIS ON THE ELECTROCARDIOGRAM. *Robert P. Grant, M.D. and E. Harvey Estes, M.D., Atlanta, Georgia.*

From the Departments of Physiology and Medicine, Emory University School of Medicine.

The effect of digitalis on the ECG has been recognized as one which tends to reduce the ventricular gradient to zero. In effect this means that the T wave comes to have an opposite direction but equal magnitude to the QRS. The development of methods for studying instantaneous vector components of ECG deflections and determining magnitude and direction of electrical forces of the QRS and T in space have made study of some of the properties of this phenomenon possible.

Descriptively it can be said that the T vector on digitalization gradually shrinks without changing direction and the potentials of repolarization become evident in the S-T segment. This is manifest as an S-T vector at 180° from the QRS vector. Thus by vector methods the detection of abnormal T waves (an abnormality in direction of the gradient) is often possible in the presence of digitalis ST and T effect.

The undigitalized subject on passive breath holding shows a decrease in size of the T vector but the QRS-T angle remains relatively constant. However, a partially digitalized subject showing only a slight decrease in magnitude of the T vector with no discernible ST component develops the pattern of complete digitalization—that is the resultant ST-T vector at 180° from the QRS—with this maneuver. A continuous positive pressure breathing apparatus was constructed to study this phenomenon more closely. It was found that the development of digitalis effects in the partially digitalized

subject was related to changes in intrapulmonary pressure rather than changes in arterial oxygen saturation. Other procedures which alter hemodynamics were studied in relation to the changes they produced in the effect of digitalis on the ECG.

It is evident that digitalis sensitizes the myocardial membrane to quite delicate variations in intrapulmonary pressure. Whether this is due to an alteration in the gradient of pressure across the myocardium or to other mechanisms has not yet been established. The study suggests that hemodynamic and respiratory factors such as dyspnea will play a part in the degree of digitalis effect seen in the ECG.

STUDIES ON THE EFFECTS OF DIGITOXIN ON THE COAGULATION MECHANISM. *William C. Levin, M.D. and A. Ruskin, M.D., Galveston, Texas.*

From the Department of Internal Medicine and the Hematology Research Laboratory, the University of Texas Medical School.

Heparin tolerance studies were performed on eleven patients all of whom had no evidence of cardiac decompensation or thrombo-embolic disease. These studies were made before and after the patients had received a full digitalizing dose (1.6 mg.) of digitoxin. The tolerance studies were done as described by de Takats, and by a modified method, using the Lee and White coagulation time technic. The heparin tolerance curves displayed no significant changes following digitoxin when the capillary tube technic was used. Seven of the same eleven patients showed no significant changes in heparin tolerance after digitoxin when the Lee and White method was used. Two showed decreased tolerance and two showed increased tolerance to heparin after digitoxin, using this same technic.

The problem was studied further by performing prothrombin times on nine similar patients before and after administration of digitoxin. There was no significant change in the prothrombin time. These subjects were then given dicumarol in doses of 300 mg., 200 mg and 100 mg. on three successive days while on a maintenance dose of digitoxin (0.2 mg./day). In all instances the response to dicumarol was considered normal.

Three other patients whose prothrombin activity was kept between 10 per cent and 30

per cent of normal by the administration of the necessary doses of dicumarol were given digitalizing doses of digitoxin. There was no rise of prothrombin activity above the aforementioned levels following digitoxin.

The impression has been gained that these data do not support the thesis that digitalis promotes coagulation of the blood.

CRITICAL APPRAISAL OF ANTICOAGULANT THERAPY WITH HEPARIN AND DICUMAROL IN CORONARY ARTERIOSCLEROSIS WITH MYOCARDIAL INFARCTION BY COMPARISON WITHIN PROGNOSTIC CATEGORIES. *Robert H. Furman, M.D., Robert G. Gale, M.D., F. Tremaine Billings, Jr., M.D. and George R. Meneely, M.D., Nashville, Tennessee.*

From the Department of Medicine, Vanderbilt University School of Medicine and the Research Laboratory, Thayer Veterans Administration Hospital.

It is possible to sort patients with myocardial infarcts into categories according to the nature of the clinical manifestations observed. When this is done, patients in some categories fare very much worse or very much better than would be expected of the group as a whole. It would appear that comparison within prognostic categories was a more valid method of investigating the effect of anticoagulant therapy than by application of overall mortality rates. The purpose of this presentation is to report certain tentative conclusions which may be inferred from a preliminary analysis of 343 patients with attacks of myocardial infarction of whom 240 were a sample from our past experience, eighty-two had recently observed episodes treated with anticoagulants and twenty-one had recent episodes not so treated. These three groups of patients were comparable as to age, sex and severity of illness.

The mortality among controls was 40 per cent, among anticoagulant-treated patients 16 per cent. Closer scrutiny showed, however, that the reduction was almost entirely due to a reduction in mortality among those suffering from first attacks. The outlook for the patient in an attack other than the first attack was not modified by anticoagulant therapy. Thrombo-embolic manifestations among our control patients were uncommon. We could not, therefore, account for lowered mortality on the basis of prevention of peripheral or pulmonary thrombo-embolic

phenomena. Among control patients with congestive heart failure the outlook was ominous but anticoagulant therapy sharply improved the gloomy prognosis from an expected mortality of 55 per cent to 17 per cent. Even in the presence of a shock-like syndrome, the mortality was lowered. So also in the case of cyanosis or leukocytosis the application of anticoagulants resulted in sharply lowered thirty-day mortality.

CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION IN NEUROSYPHILIS. *John L. Patterson, Jr., M.D. (by invitation) and Albert Heyman, M.D., Atlanta, Georgia.*

From the Departments of Physiology and Medicine, Emory University School of Medicine.

The cerebral blood flow in a group of patients with neurosyphilis has been determined by means of the nitrous oxide technic of Kety and Schmidt. Cerebral oxygen consumption has been calculated utilizing the flow data and the arteriovenous (internal jugular) oxygen differences.

In patients with paresis and meningovascular syphilis the cerebral blood flow was found to be below the normal mean in almost every instance. In some patients with paresis the cerebral blood flow was decreased by as much as 50 per cent of normal. Cerebral oxygen consumption was reduced in both groups of patients but the reduction was considerably greater in paresis. With few exceptions the cerebral blood flow and oxygen consumption were normal in asymptomatic neurosyphilis.

The effect of penicillin and fever therapy was determined in a number of these patients. Following treatment the mean cerebral blood flow was essentially unchanged in paresis but was significantly increased in meningovascular syphilis. The cerebral oxygen consumption increased markedly both in patients with paresis and in those with meningovascular syphilis. The changes in cerebral blood flow and oxygen consumption in a given patient could be correlated to some degree with the clinical improvement.

These alterations in cerebral blood flow and oxygen consumption are believed to be the result of the vascular and parenchymal changes produced by syphilis of the central nervous system.

A COMPARISON OF GLOMERULAR AND TUBULAR PLASMA FLOW IN MAN. *Walter H. Cargill, M.D. (introduced by James V. Warren, M.D.), Atlanta, Georgia.*

From the Departments of Medicine and Biochemistry, Emory University School of Medicine.

The rate of plasma flow through the kidney may be calculated from the rate of excretion of a substance and the concentration of this substance in arterial and renal-venous plasma,

according to the formula $\frac{UV}{A - R}$. The available

evidence indicates that inulin is excreted entirely by glomerular filtration, whereas the excretion of sodium para-aminohippurate is accomplished largely by active tubular transfer. The value for renal plasma flow obtained from inulin concentrations should represent, therefore, only the volume of plasma which perfuses the glomeruli, and that derived from para-aminohippurate clearance and extraction represents the flow through both glomeruli and tubules, predominantly the latter. These determinations therefore may be designated glomerular plasma flow (GPF) and tubular plasma flow (TPF).

We have compared glomerular and tubular plasma flows in normal subjects and in patients with glomerulonephritis or nephrosclerosis who had varying degrees of renal impairment. Samples of renal venous blood were obtained by the technic of intravenous catheterization.

Close agreement between GPF and TPF was found in all subjects, indicating that inulin is neither metabolized nor stored by the kidney and that there is no extensive dissociation of glomerular and tubular blood supply even in advanced renal disease.

MECHANISMS OF PHASIC PAINS INDUCED BY COLD. *E. Charles Kunkle, M.D., Durham, North Carolina.*

From Duke University School of Medicine.

Cyclic pain and other phenomena induced by immersion of a finger in cold water have been analyzed in 130 experiments upon twenty-four adult subjects. At a water temperature of 0°C. the initial pain, a deep cold ache, rises usually to a high intensity in three to five minutes, at which time plethysmographic records indicate the arteries of the immersed finger are extremely constricted. This "first" pain then slowly

subsides, an "adaptation" accompanied by progressive impairment of sensation in the chilled digit and by a partial release of the local vasoconstriction.

The onset of a "second" pain after eight to twelve minutes is foreshadowed by a brisk further increase in local circulation and by a rapid return of sensibility in the digit. At the peak of "second" pain, a burning ache, the digital pulse amplitude is well above control levels. With the rapid subsidence of this pain, the pulse amplitude falls to normal and the finger remains fully sentient.

If the digit remains in the bath thereafter, for periods up to two hours, additional recurrences of pain are noted; each such phase is usually brief and mild accompanied by moderate vasoconstriction. Upon removal of the finger from the bath after "first" or "second" pain, a transient but intense "after" pain is commonly noted, accompanied by hyperemia and similar in quality to "second" pain.

The analysis of vascular components in the pain mechanisms is aided by interruption of circulation to the hand at strategic points in the cycle. The data suggest that vasoconstriction, which previously had been assumed to be in itself the source of cold pain, is relevant mainly in promoting cooling of the finger and thus intensifying the pain stimulus. It is also inferred that "adaptation" to "first" pain is a complex of reactions involving (1) impairment of sensory transmission and (2) rewarming of chilled tissues by release of vasoconstriction. The return of full function in sensory nerves earlier numbed by cold leads to "second" pain; an additional contribution to this pain may come from excessive dilatation of digital arteries. These phenomena are relevant to the experience of the patient with Raynaud's disease in whom, because the digits are prone to vasospasm, there is unusual vulnerability to pain during and after chilling.

CINERADIOGRAPHY IN MAN. *J. V. Warren, M.D., H. S. Weens, M.D. (by invitation), R. L. McWhorter, Jr., M.D. and H. L. Murray, M.D., Atlanta, Georgia.*

From the Departments of Physiology, Radiology and Medicine, Emory University School of Medicine.

The development of a means for recording an x-ray image by motion pictures, cineradiography, has been hampered by various technical

difficulties. Since many body activities occur quite rapidly, slow motion filming is desirable but increases the technical problems. Recent reports from this laboratory have described a cineradiographic method for the study of small animals. This technic has been modified to provide a relatively simple and practical method for cineradiography in man.

The so-called indirect method is employed in which the image produced on a fluoroscopic screen is photographed with a motion picture camera. An x-ray generator of high energy output is used in conjunction with a heavy duty rotating anode tube. The fluoroscopic screen is incorporated in one side of a telescopic, light-tight wooden box. The opposite side of the box is a sheet of lead through the center of which there is an aperture for the camera lens. Both 16 and 35 mm. motion picture cameras with large aperture lenses and high speed film have been used. This apparatus permits the photographing of the fluoroscopic image in an illuminated room and gives considerable flexibility in operation. Measurements have shown that the radiation received by the patient is not excessive providing the exposure is not prolonged.

Studies already carried out demonstrate several possible fields of application. The motions of bones and joints can be clearly recorded. By making slow motion films during the swallowing of a barium mixture, the passage of the bolus through the pharynx and esophagus can be observed. Cine-angiocardigrams (films of the heart and great vessels during the injection of contrast media) have also been made. In addition to providing a means of actually visualizing the passage of the material through the heart and great vessels frame by frame analysis provides a means of accurately studying various events in the cardiac cycle.

DIFFERENTIATION OF THE CONTINUOUS MURMUR OF PATENT DUCTUS ARTERIOSUS FROM THE TO AND FRO PULMONIC MURMUR. *A. L. Hyman, M.D., Louis Levy, II, M.D., Edgar Hull, M.D. (by invitation) and Richard Bagnetto, M.D., New Orleans, Louisiana.*

The presence of a patent ductus arteriosus must be considered when a systolic and diastolic murmur are heard at the second left intercostal space; however, there are certain characteristics which differentiate the continuous murmur of a

patent ductus arteriosus from the to and fro murmur produced by pulmonary artery or valvular disease.

The to and fro murmur heard in five patients with pulmonary valve or artery disease is contrasted with the continuous murmur produced by patent ductus arteriosus. These patients had cardiac catheterization and peripheral arterial oxygen studies in addition to routine work-ups including sound tracings. One patient had congenital isolated pulmonary valve stenosis and insufficiency, two had acquired congenital isolated pulmonary valve stenosis and insufficiency, one on a rheumatic and one on an endocarditis basis, and two patients had pulmonary artery aneurysms.

The machinery murmur of a patent ductus arteriosus is continuous throughout systole and diastole in most cases. It may occasionally fade out in late diastole; however, it should almost always tend to continue past and obscure the second sound. On the other hand, a to and fro murmur found in pulmonary artery and valvular disease consists of a systolic crescendo murmur, usually a second sound, and a diastolic decrescendo murmur with a pause between the two phases. The continuous murmur tends to have the same quality throughout with increased intensity in systole, whereas the to and fro murmur usually tends to be low-pitched and rough in systole and high-pitched and blowing in diastole.

PRELIMINARY STUDIES ON THE ASSAY OF LACTOGENIC HORMONE IN HUMAN URINE.

*Richard L. Coppedge, M.D. (by invitation)
and Albert Segaloff, M.D., New Orleans,
Louisiana.*

From the Departments of Physiology and Medicine of the Tulane University of Louisiana and the Endocrine Research Laboratories of the Alton Ochsner Medical Foundation.

Riddle and Bates have shown that the weights of excised crop-sacs of pigeons are proportional to the amount of systemically administered prolactin. The local method of Lyons, modified by Hall, compares the two crop-sacs of the same pigeon after intradermal injection of a known prolactin standard over one sac and an unknown over the other.

In our procedure, prolactin was extracted from twenty-four-hour urine specimens by multiple acid-alcohol precipitations and dialysis against 0.5 per cent saline. Assay by the local technic, at first the only method used, did not prove entirely satisfactory as the prolactin response was often obscured by a non-specific inflammatory reaction. Systemic assay, employing intravenous injection, gave results which correlate satisfactorily with those of local assay. In both methods injections were made daily for four days and the animals were sacrificed on the fifth day.

Local assays on four normal women revealed a urinary prolactin excretion of < 25 I.U. to 100 I.U./24 hours, with no consistent change accompanying various phases of the menstrual cycle; of these subjects two nulliparae were consistently lower than two who had borne children. One male had values of 50 and 100 I.U./24 hours.

Assays by the local technic revealed assayable values within the range of our few normals in three cases of pituitary tumor, in hirsutism (two cases), precocious puberty (one) and advanced breast carcinoma (five). Low values were obtained in three patients with fibromyomata uteri, in endometriosis (one), bilateral testicular atrophy (one), Sheehan's syndrome (one) and breast carcinoma (two). Elevated values were found in Cushing's syndrome due to adrenal carcinoma (one case), precocious puberty (one), chronic cystic mastitis (one) and breast carcinoma (two).

Case Reports

Chronic Pancreatitis*

RUSSELL D. WILLIAMS, M.D.

Monterey, California

PANCREATIC disease is still surrounded by mystery. The present concept of the pathologic physiology of acute pancreatitis is at best a working hypothesis. The changes seen at operation vary from slight edema to severe fat and vascular necrosis and are thought of as resulting from varying degrees of duct obstruction. Such obstruction, with or without attendant infection, is considered responsible for the escape of lipolytic and proteolytic enzymes into the interstitial tissue of the gland and into the surrounding tissues.

The causes of the obstruction are frequently obscure. Evidence to support the "common channel" hypothesis, which is anatomically possible in about 50 per cent of cases, is not often found. Metaplasia of the epithelium of the ducts apparently does not answer the question either in the majority of cases although perhaps it is not looked for with sufficient diligence. An unduly thick and viscous type of mucus has been shown to cause the obstruction in the chronic cystic fibrosis of infants and children but has never been demonstrated in adults.

The exact mechanism by which the enzymes escape from the ducts is equally obscure. Pressures built up by glandular secretions are not enough to produce rupture of even the smallest ducts. The answer to the problem may lie in the fact that the active part of the enzyme is loosely bound to a large colloidal carrier. Ågren¹ has suggested that under conditions of increased acidity, increased enzyme concentration and increased pressure it is possible that the small active group becomes

dissociated from its carrier and passes through membranes into the capillaries and into the interstitial spaces where it then finds another carrier. Such a method of passing through tissue barriers has been demonstrated in other enzyme systems.

Chronic pancreatitis appears in forms even more difficult to bring together into a single dynamic concept. Recently Comfort² has written an excellent review of a syndrome which he calls chronic relapsing pancreatitis. The term indicates repetitive attacks of pancreatic pain, with or without such signs of acute inflammation as fever, leukocytosis and elevated serum amylase or lipase. Sooner or later the results of destruction of the gland may occur in the form of steatorrhea, diabetes or calcification. This picture describes the natural history of an organ affected by disease processes. It focuses attention on a clinical syndrome rather than on individual pathologic entities and thus corresponds to the concept of Bright's disease as contrasted with the various forms of nephritis.

Certain types of chronic pancreatitis vary sufficiently from each other to warrant a tentative separation. Although an obstructive factor may underlie all forms, variations in the type and location of the obstruction may be responsible for varying clinical and pathologic pictures. Thus there are the various kinds of cysts which are sufficiently large to become surgical problems. There is the mass of fibrous tissue which simulates carcinoma not only in its clinical manifestations but even at operation and on frozen section. There is the pancreatic lithiasis

* From the Department of Medicine, Veterans Administration Hospital, Topeka, Kan. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn.

which behaves very much like its counterpart, cholelithiasis, in that symptoms may be present or absent. And there is the childhood form known as chronic cystic fibrosis.

Recently another type has been separated tentatively from the hodgepodge of chronic diseases of the pancreas. This has been termed "disseminated calcification of the pancreas," and Wirts and Snape³ have written a good review of the subject. In general the symptoms and signs are those of chronic relapsing pancreatitis: attacks of epigastric pain, manifestations of insufficiency of various functions of the gland and evidence of fine stippled calcification. The picture may differ, however, from the usual pancreatic lithiasis in several ways: (1) Its incidence is much lower. The incidence of pancreatic lithiasis of all types is hard to determine because it will vary with the interest of the observer. Thus in several large series of routine autopsies the figures are given as from 0.04 per cent to 0.1 per cent whereas if x-rays and careful dissection are done the incidence rises to something over 5.0 per cent. Only twenty-five cases of "disseminated" pancreatic calcification have been reported as such, but this is not a true measure of its incidence as some authors² have not considered it a separate entity. (2) It has been stated that the calcification occurs at a somewhat younger age than the usual pancreatic lithiasis. Again exact figures are hard to gather because the age at which symptoms began is not always given in reports. (3) The calcification as seen by x-ray is a diffuse stippling or mottling involving various portions of the gland. It is thus quite different from the typical pancreatic lithiasis which is described usually as multiple calculi irregular in shape and size, occasionally as single calculi or multiple faceted calculi and rarely as casts of the ducts. (4) Biopsy and autopsy specimens show extensive replacement of the parenchyma by fibrosis, with varying degrees of dilatation of the larger ducts and more constant dilatation of the finer ducts. The minute calculi extend

throughout the duct system into the finest radicles. Occasionally larger calculi are present in the larger ducts. Further careful histologic studies will be necessary to determine whether this picture actually represents a disease process distinct from the more usual type of lithiasis and from other forms of chronic pancreatitis without calcification. For the present it would seem worth while to consider it a different disease process.

The following case is an example of this type of chronic pancreatitis. It illustrates almost all the points which various authors have made about chronic pancreatic disease. In particular it shows the difficulties of establishing the diagnosis and how the effect of long continued "hidden" pain can produce a picture practically indistinguishable from a psychoneurosis.

CASE REPORT

D. M., a thirty-five year old white male, was admitted to the Veterans Administration Hospital, Topeka, Kansas, in August, 1946 because of a psychosis due to bromide intoxication.

His past history was not remarkable. There had been the usual childhood diseases, including pertussis and mumps, and the usual number of respiratory infections. He had been somewhat "scrawny" but in general his physical health had been good. Emotionally, however, his childhood had been rather stormy. His parents separated when he was eight months old and he lived with his mother and grandmother. There were frequent arguments and frequent moves from one place to another. Later, during the depression years, the patient worked at many different jobs and was unemployed at times. He was twice married. The war came along when for the first time he was beginning to have a feeling of some security in his job and married life.

At the Army induction examination in 1942 the rack of blood tubes was dropped and no attempt was made to recall the men. In 1943 a Wassermann test taken during a routine examination was positive. At this time his wife and child were checked and were negative. He was advised that he had congenital syphilis and that no treatment was indicated. On separation from the Army his Wassermann test was

again positive. During his military service he made a good record and became a technical sergeant. From May, 1943 to June, 1945 he was in the China-Burma-India Theater of Operations. During this period he began to notice vague abdominal aching and discomfort. This gradually became more bothersome and was associated at times with equally vague symptoms of "indigestion." On two occasions the pain became severe enough to require hospitalization. During the second hospitalization in the spring of 1945 he received the usual investigative studies, including stool examinations and a gastrointestinal x-ray. He was told that his pain was due to a psychoneurosis.

Following his separation from the service in September, 1945, his wife left him and he became somewhat depressed. Shortly thereafter he was hospitalized with pneumonia in the Veterans Administration Hospital, Wadsworth, Kan. Here he was found to have positive serologic tests for syphilis in both blood and spinal fluid. After the pneumonia cleared he was therefore held for malarial therapy but a chronic productive cough persisted. Because of this, malarial therapy was deemed inadvisable and he was given 6 million units of penicillin.

While he was still in the hospital, he developed a pleural type of pain in his lower posterior chest, sometimes on one side and sometimes on the other. He also developed a deep, aching substernal pain, diffuse in character, and referred at times to the left shoulder and throughout the ulnar nerve distribution of the left arm. This substernal pain seemed to represent an upward spread of the abdominal discomfort which had been present to some degree for the previous two years. It was apparently related to his esophagus because fluids seemed to "stick in his throat" at times, with accentuation of the pain. Solid food was chewed well and swallowed without discomfort but he was inclined to gulp his fluids. Belching relieved the pain to some degree.

On leaving the hospital in March, 1946 his condition was as follows: he had a chronic, somewhat productive cough; mild to moderate radicular pain in the lower posterior chest; mild abdominal discomfort and mild to severe substernal aching with ulnar radiation at times; he was weak and he tired easily.

Shortly thereafter he received from a private physician a prescription for neurosine which he continued to take in steadily increasing

amounts without further medical advice. In August 1946 he became confused, quit his job and was picked up a few days later wandering about the streets of Kansas City in a completely disoriented state. He was admitted to the Veterans Administration Hospital, Topeka, Kan., two days later. He was confused and disoriented and showed bizarre neurologic findings. The blood bromide level a few days later was 175 mg. per cent. Serologic tests for syphilis were again positive in both blood and spinal fluid; the spinal fluid protein was 126 mg. per cent and the colloidal gold curve 0001221000. An x-ray of his chest showed increased bronchovascular markings in the lower lung fields which were more noticeable on the right side. Other routine examinations showed no abnormalities.

A month later the psychosis had entirely disappeared and the patient was transferred to the medical service. Here he was given another course of penicillin, 4.8 million units, and subjected to that somewhat nebulous regimen known as building-up. Because of his continued complaints, chiefly of radicular and substernal pain, he was thought to be psychoneurotic and therefore transferred to the open-ward psychiatric service. Here certain psychologic abnormalities were elicited such as fear of being watched, fear of being in groups, fear of having people behind him, undue dependency on his mother, a tendency toward alcohol and drug addictions and gastrointestinal symptoms. It was thought that these symptoms existed prior to military service and had been aggravated by his period of service. He was presented at a psychiatric conference and a diagnosis of psychoneurosis, mixed type, was made.

In November, 1946 his father died and the patient was furloughed for ninety days. He returned to the hospital in February, 1947, prior to the date of expiration of the furlough, acutely ill, coughing up a moderate amount of bright red blood and with signs of fluid at the base of his left lung. His temperature was 101°F. and the leukocyte count 16,800. Thoracentesis yielded clear brownish fluid in which a filmy reddish web formed on standing. The white cell count of this fluid was 468 with 98 per cent polymorphonuclears. Both smear and culture were negative. The reddish color of the fibrin web was due to the presence of red blood cells entangled in its strands, and the brownish fluid gave a strong positive reaction with benzidine. X-ray of the chest showed a moderate amount

of fluid on the left and the previously noted accentuation of the bronchovascular markings on the right.

In the subsequent month his chest cleared. He continued to have episodes of hemoptysis and fever but these progressively decreased in severity and after three months ceased entirely, leaving only the chronic cough which had been present for two years. At this point he presented quite a diagnostic problem. The clinical impression was that he had bronchiectasis but lipiodol bronchograms showed no evidence of this, in the lower lobes at least. Bronchoscopy, done unfortunately at a time when he was not bleeding, was equally negative. Because of the hemoptysis and pleural fluid with some blood in it plus his stay in the Orient, the possibility of paragonimiasis was entertained, but repeated searches of sputum and stools failed to show any ova. Smears and cultures were likewise negative for tuberculosis and pathogenic fungi.

Throughout this period the radicular pains in the lower posterior chest had persisted. Two bands of mild hyperesthesia were demonstrable, one from the fourth to the eighth thoracic and a more pronounced one from the eighth to the twelfth thoracic vertebrae. The substernal aching had likewise persisted and at times had been severe. The character of this pain, its radiation to the neck and left arm and its association with a feeling that a belch was imminent made it relatively certain that it was due to esophageal spasm. Repeated electrocardiograms were normal and the pain was not related to exertion. To a certain degree emotional disturbances seemed to aggravate the pain. Belladonna in doses to tolerance seemed to lessen its severity but did not abolish it. A gastrointestinal series showed normal mucosal markings in the esophagus, no evidence of cardiospasm or hiatus hernia and a normal stomach and duodenal cap. Stippled calcification was noted in the left upper quadrant and interpreted as a mesenteric node. Esophagoscopy during an episode of pain was indicated but was not feasible. Spinal fluid examination nows honed no abnormalities. Because he was obviously ill he was kept in the hospital although no diagnosis had been established.

Psychologic testing was carried out utilizing a battery of six tests. In summary, these showed a very intelligent, mildly neurasthenic person with some tendency toward compulsiveness and with some introversive trends. The presence of

an underlying psychosis or severe neurosis was not indicated. In essence he was as "normal" as most of us and probably more so than many of us. When questioned about the previously elicited psychoneurotic symptoms, such as fear of being watched and so forth, he replied, "Why, everybody feels some of those things at some time during their life. I was convinced I was a psychoneurotic, and they asked me about those things so I told them."

Toward the end of April, three months after re-admission, his sedimentation rate (Wintrobe method) rose to 30 and his white count to 15,000. Two weeks later he suddenly developed severe, constant, upper abdominal pain which lasted for ten days and then disappeared as suddenly as it had come. The patient said that this was exactly like the two previous episodes he had had in China three years previously. The pain was not sharply localized but was felt in the upper abdomen a little to the left of the midline. It radiated through to the back at about the level of the third lumbar rather more on the left side than the right. The pain was very severe at times and was relieved only by opiates. During the first five days of the ten-day period there was considerable vomiting, and intermittent nausea and severe constipation persisted throughout. For three days, about the middle of the attack, his temperature rose to 100 to 101°F. At no time was the abdominal examination remarkable, save for constant deep tenderness in the left upper quadrant.

Within a week after the sudden termination of the abdominal pain, he began to notice gradually increasing thirst and increasing frequency of urination. After two weeks this became sufficiently marked so that he complained of it. His urine sugar was then found to be 4 plus and his fasting blood sugar 348 mg. per cent. He was placed on 20 units of protamine zinc insulin which at that time adequately controlled the diabetes. It now appeared that the patient must have pancreatic disease and that this could explain the whole picture.

Further x-ray studies showed a normal functioning gallbladder and normal renal shadows by the intravenous method. A small intestinal study revealed a marked abnormality in the jejunum and ileum, with segmentation, loss of mucosal markings, areas of spasm and of dilatation, "puddling" of the barium and slight delay in gastric emptying. Films in various positions showed the previously noted area of

diffuse mottled calcification in the left upper quadrant and in addition another similar area overlying the second lumbar vertebrae just within the curve of the first and second portions of the duodenum. (Fig. 1.) The two areas of disseminated calcification lay, therefore, within

TABLE I

RESPONSE TO SECRETIN—THE FIGURES REPRESENT THE TOTAL OUTPUT FOR AN EIGHTY-MINUTE PERIOD FOLLOWING INTRAVENOUS INJECTION OF SECRETIN, 1 UNIT PER KG.

	Vol. cc./Kg.	Bicar- bonate m.Eq./ L.	Trypsin (units/ Kg.)	Amy- lase*	Lip- ase†
Control					
Case...	5.3	118	1 45	9 4	1570
Patient...	1 2	12	0.24	0 49	89

* Amylase figures represent Gm. of dextrose liberated.

† Lipase figures represent the volume of N/10 base required to neutralize butyric acid liberated from tributyrin substrate.

the area occupied by the pancreas, one in the region of the head and the other somewhere beyond the mid-portion. Repeated stool examinations showed a rather soft and mush-stool of normal color and in no sense foamy or oily. Microscopic examinations, however, constantly showed a moderate amount of free fat, numerous fatty acid crystals and frequent particles of undigested meat fibers. Blood cholesterol was 261 mg. per cent; calcium, phosphorus and phosphatase determinations were within normal limits; cephalin-cholesterol flocculation test was negative. Blood amylase and lipase determinations were done repeatedly, particularly at the onset of subsequent attacks, but they were always normal. A secretin test showed very marked diminution in all the functions of the gland. The test was carried out according to the method of Ågren,^{1,4} using a double lumen tube so as to maintain constant gastric as well as duodenal aspiration. This not only eliminates the stimulating effect of gastric acid on pancreatic secretion but also provides a means of checking on any possible reflux of duodenal contents into the stomach. (Table I.)

He was given pancreatin 10 Gm. daily, large doses of the fat-soluble vitamins, and a "sprue" diet high in protein and free sugar and low in starch and fat. At any given time the diabetes

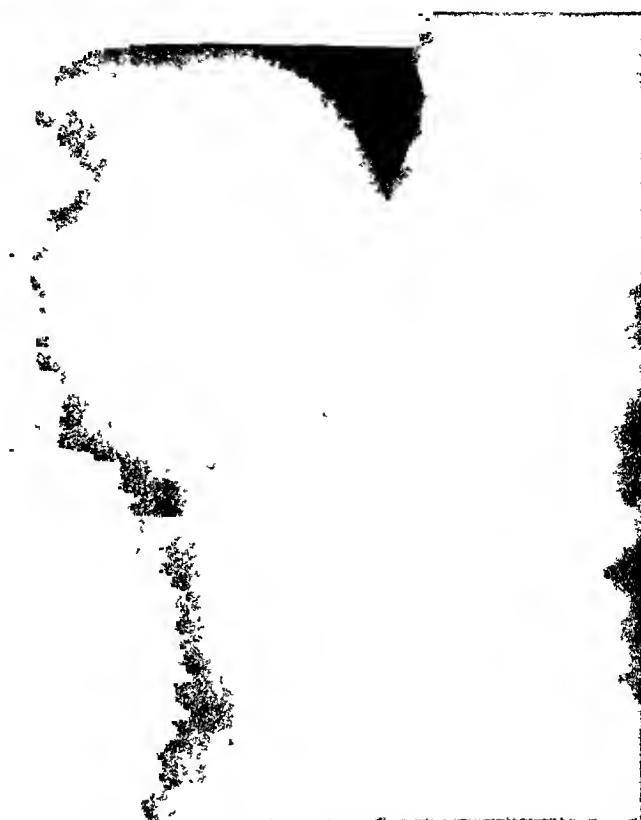


FIG. 1. Right anterior oblique view showing diffuse stippled calcification in the head and body of the pancreas.

could be well controlled with insulin, but successive bouts of abdominal pain, anorexia and vomiting necessitated frequent drastic shifts in both diet and insulin.

He was again furloughed in September, 1947 but another attack of pain in October necessitated hospitalization this time in the Veterans Administration Hospital, Montgomery, Ala. Physical findings were essentially unchanged and a bronchogram was again normal. Bilateral sympathetic block with procaine from the tenth thoracic to the first lumbar vertebrae, inclusive, afforded complete relief of pain for three hours. A subsequent block from the eighth to the tenth thoracic vertebrae gave very little relief.

The patient returned to the Veterans Hospital, Topeka, in December, 1947, with the clinical picture unchanged save that he now required 40 to 50 units of insulin to control his diabetes. Abdominal pain continued to occur at intervals of a few weeks. Between attacks he was asymptomatic save for the constant mild back pain. For several days he had swelling and tenderness of both submaxillary glands as well as a rather dry mouth. He stated that this was the third such episode. X-rays of the glands showed no abnormalities.

COMMENTS

Without entering into a discussion of all the problems concerned, I would like to stress certain points:

1. Pancreatic pain may be present for years without demonstrable abnormalities revealed by routine methods of examination. There are several reports in the literature of patients who were erroneously considered to be psychoneurotic, a mistake which is particularly likely to occur when emotional disturbance is suggested by the life history, or by the presenting personality of the patient.⁵⁻⁹ Pratt¹⁰ states that he returned five such patients to referring physicians as psychoneurotics before he became sufficiently aware of the hidden nature of pancreatic disease. The vagaries of the pain itself contribute to the likelihood of such an error. It is described as characteristically a deep boring epigastric pain occurring in attacks over months or years, with nausea and vomiting, usually unassociated with meals, often aggravated by alcohol and requiring morphine for relief. But the pain may be a constant dull ache in the epigastrium or left upper quadrant or it may be felt primarily in the back. It may be in the right upper quadrant and may radiate to either of the lower quadrants. Involvement of a particular portion of the gland is presumably responsible for these distributions. Thus disease in the tail of the pancreas is often associated with pain which radiates upward into the substernal region and the ulnar distribution of the left arm. In some instances eating will aggravate the pain, and occasionally the associated reflex disturbance of the gastrointestinal tract may be so striking that comparatively mild pancreatic pain is overlooked. The pain is usually not a colic but a steady plateau type of deep pain. What actually causes the pain remains a complete mystery. A suggestion arises from pathologic studies of the gland which have shown a perineural inflammatory process at times.

2. The frequent association of alcoholism with chronic pancreatic disease is often commented on. Among alcoholics in gen-

eral, evidence of pancreatic disease is more frequent at autopsy than among non-alcoholics. It remains a moot question as to whether alcoholism has a specific effect on the gland or is damaging because of associated vitamin deficiencies. Alcohol is said to be a potent stimulus to pancreatic secretion but I am aware of no studies to show whether its effect is primary or secondary due to its stimulating effect on gastric acid secretion.

3. Several authors have stressed the fact that calcification may not be seen on a routine "flat plate" of the abdomen. In this instance the calcification in the body of the pancreas was dismissed, first as barium in the jejunum and later as mesenteric nodes. The calcification in the head overlay the vertebral bodies and was not seen. Oblique and lateral films are necessary as well as postero-anterior films taken with specific technics to bring out small areas of calcification. Most students of the problem consider stone formation the result and not the cause of the disease. This accords with general views on stone formation elsewhere in the body but does not imply that the presence of the stone may not be responsible for subsequent further damage.

4. The abnormal small intestinal pattern by x-ray, which goes by the very inadequate name of "deficiency pattern," has been described many times, particularly by Golden¹¹ and Mackie.¹² It is found characteristically whenever fat absorption is impaired for any reason, whether due to enzyme deficiency in pancreatic disease, bile deficiency in obstructive jaundice or "X" deficiency in sprue. But at times it is also found in such apparently unrelated conditions as experimental B complex deficiencies, nephrosis, mesenteric lymphadenitis and intra-abdominal carcinoma. In dogs it can be produced by plasmapheresis. In rats a state of rage is accompanied by the "deficiency pattern." It occurs normally in the newborn infant. Recently it has been found to occur very frequently in gastrointestinal disturbances of psychogenic origin. In certain instances

prostigmine will produce a return to a normal pattern. The so-called "deficiency pattern" therefore represents what is probably a disturbance in motility resulting from many different causes.

5. Chronic cystic fibrosis of the pancreas is a disease of infancy and childhood. Clinically, the patients are divided into three groups; (1) those dying within the first few weeks of life of meconium ileus, (2) those dying in the first year of bronchitis, bronchiectasis or pneumonia but with nutritional disturbances in the background and (3) those surviving longer and developing the picture of coeliac disease to a greater or lesser degree but dying of respiratory disease. (Pancreatic deficiency due to congenital abnormalities such as stenosis or atresia of the duct forms a separate group.) Pathologically, these cases show dilatation of the ducts, inspissation of secretions, acinar atrophy and fibrosis. The liver shows the fatty changes so frequent in pancreatic disease and rarely an unusual form of biliary cirrhosis which resembles the pancreatic changes. Inspissation of secretions in ducts and acini of other glands is found if specifically looked for. It is found in the salivary glands, in the mucous glands of the tracheobronchial tree, esophagus, and gall-bladder and is "so frequent it must be regarded as a characteristic feature of the disease."¹³ The theory of a primary disorder in glandular function is supported by the fact that cases of proven pancreatic deficiency with the coeliac syndrome may show at autopsy only inspissation, without fibrosis, atrophy or dilatation of the ducts. Blackfan has suggested that this syndrome may be due to an abnormality of the parasympathetic system, with production of an unusually thick secretion in various glands.

The inference that the primary changes in disseminated calcification of the pancreas occur in the small ducts, as evidenced by the location of the calcium deposits, has suggested to Wirts³ and others that this may represent a milder and long continued form of the childhood disease. The variations in

the childhood form which have been pointed out, particularly the third or oldest group, suggest that logically there should be a fourth group in which the disease process goes at an even slower rate, producing symptoms only in later life. Bronchiectasis has been looked for with this in mind but has not been found. Pulmonary disease in general, however, occurs in high incidence in the disseminated calcification group.

Certain symptoms in the present case support such an analogy. Bronchiectasis was never demonstrated, in the lower lobes at least, but the clinical picture was very characteristic. Certainly the patient had had a chronic lower respiratory tract abnormality for the previous two years. Likewise, the bouts of submaxillary gland swelling with episodes of dryness of the mouth suggest an abnormality of the salivary glands.

It was believed that syphilis was not responsible for the pancreatic disease in this case for several reasons, chief among them being the absence of syphilis in similar cases.

6. The therapeutic management of the trio of (1) episodic pain with vomiting, (2) pancreatic deficiency and (3) diabetes is difficult. Addiction is a constant problem because significant relief of pain is obtained only with generous doses of opiates. The various antispasmodic drugs, even in large doses, are of no use whatever. Fat absorption can be materially increased by pancreatin; the industrial detergents may prove of equal or greater value.¹⁴ Diet and hence insulin requirements may be in a constant state of flux if attacks with vomiting occur with any frequency. The only reported case in which the rational procedure of severing the sensory fibers of the pancreas was carried out is that of Reinhoff and Baker.¹⁵ Bilateral sympathectomy from the fifth thoracic to the second lumbar ganglion, together with vagotomy, provided complete relief of pain and changed a chronic addict of years' standing with a "psychopathic personality" back into a useful citizen. To date our patient has refused

operation although his course for the past two years has been that of a totally incapacitated invalid.

SUMMARY

A case of disseminated calcification of the pancreas is reported. The question of justification for such a clinical entity is briefly discussed and its possible relationship to chronic cystic fibrosis of childhood is considered. The case demonstrates certain aspects of chronic pancreatic disease in general which are of importance, such as the frequent confusion with psychoneurosis, the ease with which the diagnosis may be missed by x-ray and the difficult therapeutic management of the fully developed symptom complex.

REFERENCES

1. ÅGREN, G., LAGERLÖF, H. and BERGLUND, H. Secretin test of pancreatic function in diagnosis of pancreatic disease. *Acta med. Scandinav.*, 90: 224, 1936.
2. COMFORT, M. W., GAMBILL, E. E. and BAGGENSTOSS, A. H. Chronic relapsing pancreatitis; study of 29 cases without associated diseases of biliary or gastrointestinal tract. *Gastroenterology*, 6: 239-285, 1946.
3. WIRTS, C. W., JR. and SNAPE, W. J. Disseminated calcification of pancreas; subacute and chronic pancreatitis. *Am. J. M. Sc.*, 213: 290-299, 1947.
4. DIAMOND, J. S., SIEGEL, S. A., GALL, M. B. and KARLAN, S. Use of secretin as clinical test for pancreatic function. *Am. J. Digest. Dis.*, 6: 366-372, 1939.
5. YASKIN, J. C. Nervous symptoms as earliest manifestations of carcinoma of the pancreas. *J. A. M. A.*, 96: 1664-1668, 1931.
6. LATTER, K. A. and WILBUR, D. L. Psychic and neurologic manifestations of carcinoma of the pancreas. *Proc. Staff Meet., Mayo Clin.*, 12: 457-462, 1937.
7. DUNPHY, J. E. Early diagnosis of carcinoma of pancreas. *Am. J. Digest. Dis.*, 7: 69-70, 1940.
8. PELNER, LOUIS. Carcinoma of pancreas—a disease that may closely mimic a psychosomatic illness. *Gastroenterology*, 8: 92, 1947.
9. RICKLES, N. K. Functional symptoms as first evidence of pancreatic disease. *J. Nerv. & Ment. Dis.*, 101: 566-571, 1945.
10. PRATT, J. H. Diagnosis of pancreatic disease. *New York State J. Med.*, 43: 1847-1855, 1943.
11. GOLDEN, R. Small intestine in vitamin B deficiency. *J. A. M. A.*, 117: 913-917, 1941.
12. MACKIE, T. T. Vitamin deficiencies and small intestine. *J. A. M. A.*, 117: 910, 1941.
13. FARBER, S. Medical progress. Pancreatic insufficiency and celiac disease. *New England J. Med.*, 229: 653, 682, 1943.
14. JONES, C. M. Fat absorption in the digestive tract and the use of surface acting agents. *Am. College Physicians*, April, 1948, San Francisco, Calif.
15. REINHOFF, W. F., JR. and BAKER, B. M. Pancreolithiasis and chronic pancreatitis. *J. A. M. A.*, 134: 20-21, 1947.

Megaloblastic Bone Marrow in Liver Disease^{*}

E. R. MOVITT, M.D.

Oakland, California

MEGALOBLASTIC bone marrow is found characteristically in patients with Addisonian anemia. The same type of bone marrow has been found also in association with macrocytic anemias of tropical and non-tropical sprue, idiopathic steatorrhea, celiac disease, pernicious anemia of pregnancy, "tropical" or nutritional macrocytic anemia and in some instances of intestinal strictures and fistulas between the different loops of bowel. Added to this list is a rare type of macrocytic anemia which has all the hematologic aspects of pernicious anemia, including megaloblastic bone marrow, but differing from the classical Addisonian anemia by absence of glossitis, achlorhydria, gastrointestinal disturbances and central nervous system involvement. The course is chronic and progressive in spite of liver therapy. The name of achrestic anemia has been given to this disorder on the hypothesis that the condition in these cases was the result of failure to utilize the antipernicious anemia principle.¹ Recently megaloblastic bone marrow has been described in certain cases of macrocytic anemia of an unknown non-dietary deficient etiology observed in infants under one year of age.²

Megaloblastic anemias may be classified etiologically into several main groups. The orientation for this classification is based on Castle's hypothesis of normal erythropoiesis. It will suffice to mention briefly that according to this hypothesis the maturation of the primitive erythroblasts is dependent upon the presence of an "anti-anemic principle" which is elaborated in the stomach from the interaction of an "intrinsic

factor" secreted by the gastric mucosa with an extrinsic factor present in certain protein constituents of the diet. The anti-anemic principle is believed to be absorbed in the upper part of the small intestine and is presumably stored in the liver. It has been suggested by some investigators³ that the liver may not act merely as a storage depot but may also participate in the final elaboration of the anti-anemic principle. It appears that some support for this assumption has recently been provided⁴ in the ingenious experiments with *Amblystoma* embryos in which removal of the liver anlage has been found to result in the development of anemia unaffected by liver therapy whereas the grafting of liver slices into the tails of the animals has resulted in restoration of hematopoiesis. The various etiologic classifications have been set up as follows: (1) Defective formation of the intrinsic factor; Addisonian pernicious anemia. (2) Defective intake of the extrinsic factor; nutritional anemias ("tropical" anemias). (3) Defective absorption of the anti-anemic principle; tropical and non-tropical sprue, idiopathic steatorrhea, celiac disease, gastroduodenal fistula. (4) Defective storage and/or elaboration of the anti-anemic principle; liver disease, chronic (cirrhosis). (5) Defective utilization of the anti-anemic principle? "achrestic anemia," megaloblastic anemia in children.

Such a classification is, of course, provisional, in parts highly theoretical and subject to criticism. For example, under what category should one place the megaloblastic anemia of pregnancy and puerperium? Is it due to reduced intake of the extrinsic factor consequent upon poor app-

^{*} From The Veterans Administration Hospital, Oakland, Calif. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed and conclusions drawn by the author.

tite and nausea? Is it caused by impaired absorption of the anti-anemic principle from the small intestine due to altered hydrogen ion concentration of its contents? Or is it due to only a relative decrease in the amount of the available anti-anemic principle conditioned by the increased demand for it by the fetus?

The assumption that the liver plays an important role in the storage and possibly even in the elaboration of the anti-anemic principle would lead one to expect the occurrence of megaloblastic anemia in chronic hepatic disease. There are numerous references in the literature to macrocytic anemia found in association with chronic diseases of the liver, particularly cirrhosis. Wintrobe⁵ has found in a series of 132 cases of different forms of liver disease the presence of macrocytic anemia in 21.9 per cent, mostly in patients with cirrhosis. The bone marrow in these cases was described as hyperplastic although the red cell count was rarely below 2,500,000 per cu. mm. Wintrobe⁶ also stated that in some patients with diseases of the liver the anemia resembled that seen in Addisonian anemia and that "oval macrocytes like those seen in pernicious anemia are found." While it is now generally recognized that macrocytic anemia may be encountered in association with cirrhosis of the liver, the frequency of this finding varies in different reports. The red cell counts usually range from 2,500,000 to 3,500,000 per cu. mm.

In a recent report⁷ on nineteen patients with liver disease nine (47.4 per cent) had macrocytic anemia, six (31.6 per cent) normocytic anemia and four (21 per cent) had no anemia. Of the patients with macrocytic anemia four had atrophic and two hypertrophic cirrhosis, two had hepatitis and one carcinoma of the liver secondary to carcinoma of the pancreas. No patient in the entire series had nucleated erythrocytes in the peripheral blood and only one, who was believed by the authors to have sprue in addition to cirrhosis, had megaloblastic bone marrow. The red cell counts ranged from 2.80 to 3.99 million and the

intensity of the anemia was not related to the severity of the liver disease, but there was a positive correlation between the degree of macrocytosis and the patient's prognosis. Of the five patients with macrocytic anemia in whom gastric analysis was done only one showed histamine-resistant achlorhydria. One had achlorhydria which was not histamine-resistant and the others had normal gastric acidity. Interestingly enough, irrespective of the outcome of the liver disease, therapy with liver extract resulted in reduction of macrocytosis and increase in red cell count. Similar observations on the response to liver therapy have been reported by other workers.^{5,11,12} In patients with cirrhosis, macrocytic anemia has been found to be more severe than in the normocytic type except in instances of massive hemorrhage from the esophageal varices. Microcytic anemia found in some patients with cirrhosis may be attributed to chronic loss of blood.

In spite of the fact that the presence of macrocytic anemia in some patients with cirrhosis of the liver has become a part of common knowledge and that megaloblastic bone marrow could well be expected to be found in some of these patients, at least on theoretical grounds, reports to that effect have been lacking. Davidson and Davis⁸ state that "The literature contains many other references to macrocytic anemia in association with cirrhosis and other diseases of the liver, *but we know of no reports of the sternal marrow morphology in such cases.* References to the bone marrow seen at autopsy commonly refer to its being hyperplastic, but detailed cytologic descriptions do not appear to have been published." These authors make reference to the work of Higgins and Stasney⁹ and Shumacker and Wintrobe¹⁰ who have noted the production of experimental cirrhosis in animals to result in macrocytic anemia with a hyperplastic bone marrow picture stated to be similar to that seen in pernicious anemia without making it clear, however, whether it was actually megaloblastic. Davidson and Davis conclude that: "There appears,

then, to be presumptive evidence that a megaloblastic anemia may occur in chronic severe liver disease."

The author has had the opportunity of observing megaloblastic bone marrow in a patient with cirrhosis of the liver accompanied by severe macrocytic anemia. As the patient had free hydrochloric acid on gastric analysis, intact tongue papillae and failed to respond to liver extract the diagnosis of Addisonian pernicious anemia could not be entertained.

CASE REPORT

A fifty year old white male stated that he had been in good health until five months before admission when he developed an upper respiratory infection followed by pitting edema of the legs which would be present in the evening and disappear overnight. At the beginning of his illness he was first hospitalized elsewhere and was discharged eight weeks later. On leaving the hospital he still was rather tired and the edema of the legs, although not so marked as it was at the beginning of the illness, was still present and remained without much change until admission to this hospital. There were no significant gastrointestinal symptoms. The past history was not particularly remarkable except for chronic alcoholism.

On examination the patient was seen to be a well developed but undernourished white male of about the stated age with slight icterus of the sclerae. There was no atrophy of tongue papillae. The heart and lungs were not remarkable. There was no engorgement of the cervical veins. The blood pressure was 110/80, pulse 68. The abdomen was distended, with shifting dullness in the flanks. A firm, non-tender liver could be felt by ballottement. There was moderate pitting edema of both legs and several spider angiomas over the upper anterior chest. Neurologic examination was negative.

On admission the laboratory work revealed the following findings. Urinalysis: color, clear amber; reaction, acid; specific gravity, 1.009; albumin, negative; sugar, negative; sediment, some epithelial cells, a few white blood cells. A second urinalysis was also entirely negative. Red blood cells, 1.7 million; white blood cells, 6,150 with 73 per cent polymorphonuclear leukocytes (70 segmented and 3 stab forms); lymphocytes, 23 per cent (20 small and 3 large);



FIG. 1. Photomicrograph of the bone marrow smear showing megaloblasts.

monocytes, 1; eosinophils, 3. The blood smear showed some anisocytosis and poikilocytosis with slight polychromasia and stippling in addition to an occasional Howell-Jolly body. Reticulocyte count was 3 per cent. Erythrocyte mean corpuscular volume was 118 cu. microns and mean corpuscular hemoglobin was 38.5 micro-micrograms. Icterus index was 21 units and serum bilirubin 3.0 mg. per cent. The Kahn test was negative. Blood urea nitrogen was 18 mg. per cent. Total serum protein was 4.8 Gm. per cent with albumin 2.7 Gm. per cent and globulin 2.1 Gm. per cent. Cephalin cholesterol flocculation was 2 plus in twenty-four hours and 3 plus in forty-eight hours. Bromsulfalein test showed 10.6 per cent retention of the dye in forty-five minutes (5 mg./Kg. dose). Gastric analysis after alcohol meal revealed the presence of free hydrochloric acid with 15 degrees as the maximum. Roentgenogram of the chest revealed nothing of note. The bone marrow aspirated from the sternum revealed megaloblastic proliferation,* (Fig. 1) with the following differential count: myelocytes, 15; metamyelocytes, 10; polymorphonuclears, 40; eosinophilic

*The bone marrow preparations were also studied by Dr. Harry Wyckoff (Stanford University School of Medicine) who confirmed our observations.

polymorphonuclears, 1; lymphocytes, 7; megakaryoblasts, 10; pro-erythroblasts, 4; normoblasts, 12; megakaryocytes, 1.

The patient was given liver extract intramuscularly, 30 U.S.P. units daily. However, as he failed to respond (Fig. 2) a blood transfusion

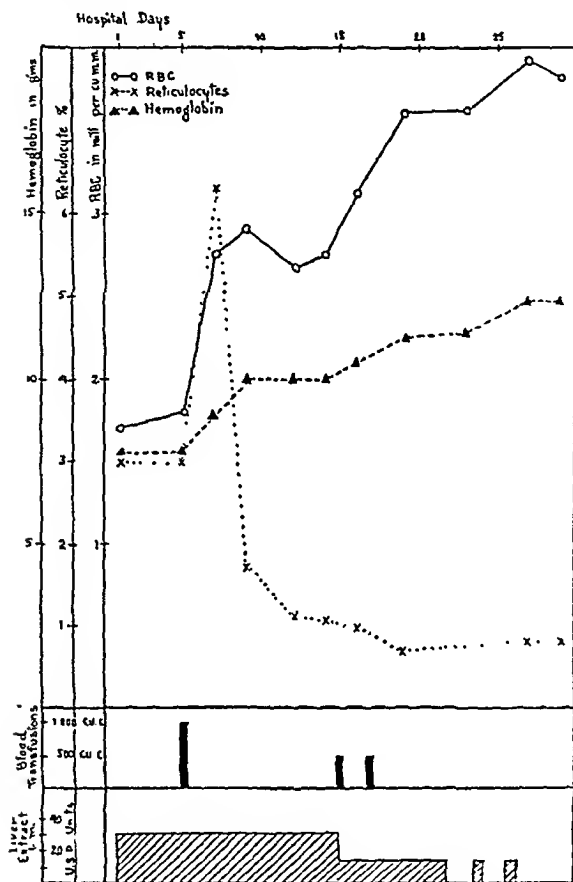


FIG. 2.

of 1,000 cc. was given on the fifth hospital day. The reticulocyte count following the transfusion went up to 6.3 per cent but soon dropped to 1.7 per cent. Liver therapy was continued in the same dosage but again without any response. Another blood transfusion of 500 cc. was given on the fifteenth hospital day and a third one of 500 cc. on the seventeenth hospital day. Further liver therapy still failed to produce any significant change.

COMMENTS

Although liver biopsy was not done, all clinical evidence pointed to a diagnosis of cirrhosis of the liver. One can only speculate about the pathogenesis of megaloblastic anemia associated with cirrhosis.

Is it due to nutritional deficiency, faulty absorption, failure of storage and/or elaboration or failure of utilization of the anti-anemic principle? Perhaps there is a number of factors operating concomitantly to produce the end result in question.

It has been suggested that patients with this disorder may suffer from the result of defective storage of the anti-anemic principle in the liver when a hepatic disease has been of a sufficient duration and extent to lead to significant depletion of the stores of hematopoietic principle. Observations have been made showing that the liver of a patient with macrocytic anemia who died of cirrhosis was ineffective in the treatment of a patient with pernicious anemia.⁵ On the other hand, other investigators have been able to demonstrate the presence of this principle in the liver of patients dying of extensive hepatic involvement.

Apparently megaloblastic bone marrow is not found in all the patients with cirrhosis and macrocytic anemia and possibly the anemia must be severe before megaloblastic arrest becomes evident on study of the bone marrow material. As severe megaloblastic anemia associated with cirrhosis is seldom encountered the unawareness of the existence of megaloblastic arrest in this condition can thus be explained.

True enough, cirrhosis of the liver and pernicious anemia may sometimes occur in the same individual. However, our patient did not appear to represent such a coincidence for the reason that he had free hydrochloric acid in the stomach, had no atrophy of the tongue papillae and failed to respond to liver therapy. The response to liver therapy in the case herein presented is somewhat difficult to evaluate. It is possible that were the treatment continued for a longer period and without blood transfusions it eventually would have proved to be more successful.

SUMMARY

Cirrhosis of the liver accompanied by severe macrocytic anemia constitutes another disease entity which can be added to the

list of conditions associated with megaloblastic proliferation in the bone marrow.*

Evidence has been presented indicating that in such cases this phenomenon does not necessarily represent the coexistence of two diseases, cirrhosis and pernicious anemia, in one and the same patient.

REFERENCES

1. ISRAELS, M. C. G. and WILKINSON, J. F. New observations on aetiology and prognosis of achrocytic anemia. *Quart. J. Med.* 9: 163, 1940.
2. ZUELZER, W. W. Folic acid therapy in the anemias of infancy and childhood. *J. A. M. A.*, 131: 7, 1946.
- * Since submission of this manuscript for publication, another case of cirrhosis of the liver with megaloblastic anemia has come under our observation. In this patient the clinical diagnosis of cirrhosis was corroborated by the liver needle biopsy which showed extensive and far advanced fibrosis. There was moderately severe macrocytic anemia with a red blood count of 2.88 million and a hemoglobin of 11.1 Gm. There were 20 per cent megaloblasts in the sternal bone marrow material which was obtained by aspiration. In contrast to the other case herein reported this patient improved rapidly on minimal amounts of liver and a high caloric, high protein diet, with the blood count returning to practically normal limits within a short period of time. The patient had free hydrochloric acid in the gastric juice and gave no history of any gastrointestinal symptoms or glossitis.
3. DAVIDSON, L. S. P. and FULLERTON, H. W. Some rare types of macrocytic anaemia. *Quart. J. Med.*, 7: 43, 1938.
4. COPENHAVER, W. M. Liver extirpation and implantation in amblystoma embryos with particular reference to blood formation. *Am. J. Anat.*, 73: 81, 1943.
5. WINTROBE, M. M. Relation of disease of liver to anemia; type of anemia, response to treatment, and relation of type of anemia to histopathologic changes in liver, spleen and bone marrow. *Arch. Int. Med.*, 57: 289, 1936.
6. WINTROBE, M. M. *Clinical Hematology*. Philadelphia, 1946. Lea & Febiger.
7. DE CASTRO, J. M. P. *Rev. de med. y cir. Habana*, 51: 423, 1946.
8. DAVIDSON, L. S. P. and DAVIS, L. J. *Advances in Internal Medicine*. P. 501. New York, 1947. Interscience Publishers.
9. HIGGINS, G. M. and STASNEY, J. Macrocytic anemia in experimental cirrhosis. *Proc. Staff Meet., Mayo Clin.*, 10: 429, 1935.
10. SHUMACKER, H. B. and WINTROBE, M. M. Morphologic changes in blood associated with experimentally produced hepatic damage. *Bull. Johns Hopkins Hosp.*, 58: 343, 1936.
11. GOLDHAMER, S. M. Pernicious anemia syndrome in gastrectomized patients. *Surg., Gynec. & Obst.*, 57: 257, 1933.
12. WINTROBE, M. M. and SHUMACKER, H. S., JR. Occurrence of macrocytic anemia in association with disorder of liver, together with consideration of relation of this anemia to pernicious anemia. *Bull. Johns Hopkins Hosp.*, 52: 387, 1933.

Epileptic Equivalents, A Cause for Somatic Symptoms

H. M. WINANS, M.D.

Dallas, Texas

THE internist is called upon many times to uncover the cause for pain. In most cases, after adequate study, the diagnosis becomes apparent but there is a small group in which no explanation seems to be at hand and in which the diagnostic study must be extended to the limits of present scientific methods. The present praiseworthy emphasis upon psychic factors in the causation of symptoms introduces one danger, namely, that when all reasonable methods of study fail to reveal the cause for the patient's symptoms there is a temptation to decide that there must be a psychogenic cause. The cases herein reported illustrate not only this point but also the difficulties occasionally encountered in making the proper diagnosis.

That pain may occur as the sole equivalent of an epileptic convulsion has been pointed out by a number of writers. Penfield and Gage¹ showed that stimulation of a cortical area caused pain in the abdomen and elicited an epileptic attack. Watts and Frazier² found that a neurogenic discharge may manifest itself through abnormally vigorous movements of the gastrointestinal musculature and that the discharge comes from the autonomic portion of the cerebral cortex. Wechsler³ reported a series of cases which led him to conclude that abdominal pain occasionally occurs in disease of the brain and may be regarded as one of its manifestations. Moore⁴ has reported a number of cases presenting paroxysmal abdominal pain as an aberrant form of epilepsy and stresses in the diagnosis the exclusion of intrinsic visceral disease, the objective evidence of cerebral organic dis-

ease or dysfunction and the effect of anti-convulsant drugs on the symptom of abdominal pain and on the electroencephalogram. The following cases are of interest in this connection:

CASE REPORTS

CASE 1. A white male was first seen at the age of thirty-six. At that time he complained of a paroxysmal cough for which he had consulted numerous physicians. He had had various studies and therapeutic efforts such as tonsillectomy, adenoidectomy and sinus treatments, all without any effect. His examination at that time was entirely unproductive of results and a bronchogram showed no evidence of bronchiectasis.

The patient was lost sight of until some eight years later, at which time he returned with a complaint of severe paroxysmal pain in the left lower thoracic region with radiation to the precordium. His interval history revealed that after consulting numerous other physicians in regard to the cough he finally became discouraged and did nothing further. The cough gradually disappeared in the course of a few years.

In the past two years the pain just described had made its appearance. A typical attack was described as a sudden and unexpected onset of an excruciating pain beginning low in the left chest and spreading to the precordium but also occasionally up the back between the shoulders and down into the abdomen. The pain was so severe that the patient feared immediate death. However, the duration was not more than ten to twenty seconds and after the attack the patient felt entirely well. He developed an intense fear of these attacks. In the beginning they occurred at intervals of a few months but recently there had been one every two or three

weeks. The patient knew of no factor which would bring on or relieve the pain. The attacks occurred under all circumstances of rest and activity.

Physical examination of this patient revealed no abnormal findings whatever nor did the

pain was rarely more than fifteen or twenty minutes, and the attacks came at intervals of a few days to several weeks. Although the attacks did not last long, the patient had developed considerable fear and apprehension regarding them. He stated that with the onset of the pain

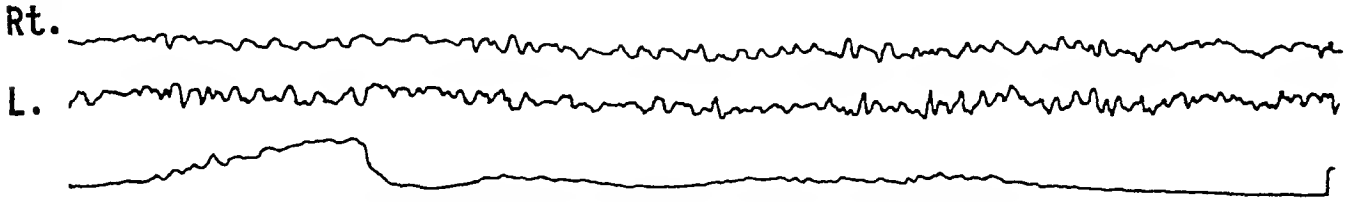


FIG. 1. Case I. Part of the electro-encephalographic tracing.

laboratory provide any further help. X-ray studies of the gallbladder and gastrointestinal tract were all non-productive. The electrocardiogram was normal at rest and after the exercise test. There were no abnormalities found in the cervical or thoracic spine.

In reviewing the history it was a temptation to assume that both the present complaint of paroxysmal pain and the cough of which he had formerly complained were due to a psychoneurosis. However, such a diagnosis would have been predicated upon exclusion since there were no definite findings to indicate that the patient had a psychoneurotic state. It was decided to have an electro-encephalographic study made. It was reported as follows: "All areas showed irregularity of the rhythm with prominent bursts of 6 to 7 per second waves. Alpha activity occurred to a moderate degree in the occipital regions, at a rate of 11 to 12 per second. Hyperventilation caused an increase of the 6-cycle waves. There was no spiking. The record was interpreted as showing a generalized dysrhythmia with paroxysmal 6 to 7 per second activity, suggestive of a convulsive state (psychomotor type)." A section of the tracing is shown in Figure 1. The patient was given phenobarbital, with complete relief of his symptoms. He has now been followed up for over a year and there have been no further attacks.

CASE II. This patient, a thirty-four year old man, presented himself with the complaint of severe, recurring paroxysms of pain in the right upper quadrant of the abdomen. These attacks of pain came on without any relationship to meals and began with a severe cramping just under the right costal margin. The pain frequently spread into the right chest and down into the lower abdomen. Nausea and vomiting sometimes were present. The duration of the

he felt a severe mental depression and had a feeling of hopelessness. He was as much concerned with these feelings as with the pain itself.

Nothing was found on physical examination. There were no abnormal neurologic findings. The accessory laboratory studies were all within normal limits as were x-ray studies of the gallbladder and the gastrointestinal tract. Perhaps the emotional disturbance in this individual provided the clue. An electro-encephalogram was made in another city and was reported to show changes typical of psychomotor epilepsy. At the last reports the patient had been doing well with use of sedatives and had had no attacks of pain in several months.

CASE III. This patient, a twenty-six year old man, presented himself because of peculiar attacks of substernal pain, rapid heart action, flushing and sweating. He had never had any serious illnesses and his family history was irrelevant. His first attack occurred while he was serving in the army in France. Although he had been through some very strenuous campaigns, at this time his unit was in a rest area and he felt that he was under no particular strain. The attack began while he was reading in his room. There was a severe substernal pain and shortly thereafter his pulse became rapid, he felt flushed and perspired freely. The pain was described as severe but not intense and the whole episode lasted only fifteen minutes. He was seen by a medical officer who sent him to the hospital where he had a thorough examination. It was not thought that this was an attack of paroxysmal tachycardia and since his examination in the hospital revealed no abnormalities he was returned to duty.

During the next six months he was released from the army and entered college. He had no other difficulties in this period of time. About

seven months from his first attack he had another one which occurred during the night and which wakened him. This was similar in every way to the first attack except that following this he was extremely depressed for the next two days. Since the first two attacks, he has had others at

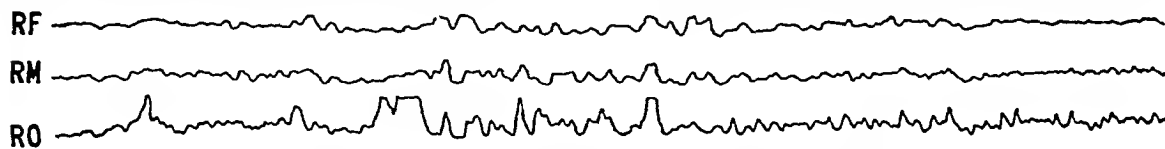


FIG. 2. Case III. Part of the electro-encephalographic tracing.

irregular intervals of from two weeks to three months. They have occurred during the daytime and also at night. The pattern has remained the same. There is first a severe substernal pain shortly followed by rapid heart action, flushing and sweating. The duration of the attack has never been longer than fifteen minutes.

Physical examination was entirely negative as were the accessory laboratory findings. X-ray studies of the gastrointestinal tract did not reveal any abnormalities and electrocardiogram was normal both before and after an exercise test. A careful psychiatric appraisal failed to reveal any information necessary for a diagnosis of a psychoneurosis. Therefore, it was decided to have an electro-encephalographic study made. This was reported as follows: "Both occipital regions showed a mixture of 16, 10, 8-9 and 7 per second waves, all decreased by light. The frontal and motor areas showed low voltage activity. On hyperventilation, random 5 to 6 per second waves appeared in all areas at one-half minute, and large 4 per second waves at two and one-half minutes. After cessation of hyperventilation, bursts of large, irregular 6 per second waves appeared in all areas for one minute. These findings were interpreted as those of a generalized dysrhythmia of non-specific nature, consistent with clinical epilepsy (although not diagnostic thereof)." A section of the tracing is shown in Figure 2.

The patient was given phenobarbital and up to this time has had no further attacks. Although he has been under observation for six months, it is still too early to be sure that no further attacks may occur due to the long period elapsing between the first and second episodes.

COMMENTS

These three cases are illustrative of the possibility that even severe pains may be the equivalent of epileptic disturbance. While

there was no evidence of organic disease of the central nervous system in these patients, as has been pointed out the same symptoms might have occurred in the presence of a number of organic involvements. It was also fortunate that there were no

abnormalities of any sort found in the study of the gastrointestinal tract. The patients may have been saved an unnecessary operation by this fact. Finally, the question might arise as to whether the symptoms were not simply those of a psychoneurotic state which in itself might have been relieved by sedatives. None of these patients, however, showed any diagnostic signs of a psychoneurosis and furthermore the uniformity of the symptomatology together with the variation in time between attacks was very much against such a diagnosis.

CONCLUSIONS

Three cases of severe pain, apparently the equivalent of an epileptic seizure, are presented. The diagnosis was made partly by exclusion and partly by findings in the electro-encephalogram. Intense fear of the attacks was present in all three patients. They were relieved by treatment with sedatives. These cases suggest that electro-encephalographic studies may be of aid in the solution of difficult problems in the diagnosis of thoracic or abdominal symptoms.

REFERENCES

1. PENFIELD, WILDER and GAGE, LYLE. Cerebral localization of epileptic manifestations. *Arch. Neurol. & Psychiat.*, 30: 709, 1933.
2. WATTS, W. J. and FRAZIER, C. H. Cortical autonomic epilepsy. *J. Nerv. & Ment. Dis.*, 81: 168-176, 1935.
3. WECHSLER, I. S. Abdominal pain as a symptom of disease of the brain. *J. A. M. A.*, 105: 9, 647-650, 1935.
4. MOORE, MATTHEW T. Paroxysmal abdominal pain: a form of focal symptomatic epilepsy. *J. A. M. A.*, 124: 561-563, 1944. II. *Ibid.* 129: 1233-1240, 1945. Aberrant forms of epilepsy: their disguise in somatosensory, psychic, and unusual motor displays. *Pennsylvania M. J.*, 48: 6, 569-572, 1945. Symptomatic abdominal epilepsy. *Am. J. Surg.*, 72: 6, 883-899, 1946.

Editorial

Vagotomy for Peptic Ulcer

INTERNISTS as well as surgeons have recently become deeply concerned about the place of bilateral vagotomy in the management of patients with refractory peptic ulcer. Physiologists for more than fifty years have been aware of the depressant effects of vagotomy on the secretory and motor functions of the stomach and more recently on the secretory function of the pancreas. But although Latarjet in 1922 included this procedure along with gastro-enterostomy in six patients with peptic ulcer, with good temporary results in five, it was not until 1943 that its application in man received special attention. In that year Dragstedt and Owens¹ reported good results from transthoracic vagotomy in two patients with duodenal ulcer. Following their lead many other surgeons have adopted the procedure, with or without accompanying gastric surgery, and have confirmed the original observations as to relief of pain, reduction in gastric acidity and, in most instances, healing of the ulcer. More recently most surgeons in order to investigate the stomach directly have accomplished the procedure subdiaphragmatically. This has permitted them at the same time to perform a gastro-enterostomy, gastrectomy or pyloroplasty; some of them adding gastric surgery only when an obstruction was found, but others, whether or not obstruction was demonstrable, in an attempt to prevent the gastric retention that so commonly follows vagal section.

¹ DRAGSTEDT, L. R. and OWENS, F. M. Supradiaphragmatic section of the vagus nerves in treatment of duodenal ulcer. *Proc. Soc. Exper. Biol. & Med.*, 53: 152, 1943.

Many thousands of patients with peptic ulcer have now been subjected to vagotomy, with or without gastric surgery, and apparently with satisfactory results in most instances. It should be appreciated, however, that as yet the duration of postoperative observation of these patients is relatively short and that many therapeutic procedures received with equal enthusiasm have subsequently been abandoned, or at least restricted in their application, because of ultimate complications. One cannot but wonder, therefore, if the time has not come to abandon temporarily the ready employment of vagotomy until a longer period of evaluation of results is available. This would seem especially indicated in view of the data available in the physiologic literature and of the frequent reports of unsatisfactory results that are already appearing in the clinical literature.

In the late nineteenth century Pavlov² demonstrated that dogs subjected to complete vagotomy developed stagnation in the stomach leading to death. Thomas and Komorov³ on the basis of animal work regard complete section of the vagi as incompatible with life and explain long survival after the modern operation in man on the basis of incompleteness of the section. Crider and Thomas⁴ have also shown that after vagotomy the output of pancreatic enzymes is reduced by 50 per cent or more.

² PAVLOV, I. P.³

³ THOMAS, J. E. and KOMOROV, S. A. Physiological aspects of vagotomy. *Gastroenterology*, 11: 413, 1948.

⁴ CRIDER, J. O. and THOMAS, J. E. Secretion of pancreatic juice after cutting extrinsic nerves. *Am. J. Physiol.* 141: 730, 1944.

Vansant⁵ has maintained that the depression of secretion produced by vagotomy in the dog is transitory, the acidity returning to a normal level after two or three years. All workers agree as to the depression of the motor function of the stomach, some reporting prolonged troublesome atony with almost complete absence of hunger contractions. Indeed the relief of pain almost invariably reported is presumably due to a lack of tonicity of the gastric wall.

The available reports on the results of the clinical application of vagotomy are confusing because of uncertainty as to the degree of completeness of the division of the nerve fibers and because of the other operative procedures so commonly associated with it. The insulin test of Hollander designed to determine whether or not vagal section is complete has not proved entirely satisfactory, and as yet no other method has been advanced. Some patients have previously had a subtotal gastric resection or gastro-enterostomy, some have had such an operation simultaneously and some, because of gastric retention, soon afterward. Without attempting to classify the cases one gets the impression from the clinical literature that in spite of ulcer pain relief, many of the patients, at least for months, are quite uncomfortable and certainly in some there is a failure to heal, or they develop a recurrent ulcer. Even though some type of gastro-enterostomy also is accomplished, gastric retention with a peculiar sense of fullness and sometimes vomiting often persists for a long time. Eleven of Grimson's⁶ thirty-six patients had had a previous gastro-enterostomy, five had such an operation at the time of vagotomy and five required it subsequently; yet twenty-eight had postprandial distress for at least three months, two developed hematemesis and one after twelve months had a new ulcer. Walters,⁷

in a series of eighty-three vagotomized patients at the Mayo Clinic, subsequently found one perforation, eight recurrent or persistent ulcers, and eight with troublesome gastric or intestinal stasis, including one operated upon for suspected intestinal obstruction (i.e., poor results in 20 per cent). He states that Colp in thirty-three patients had only eighteen whom he regarded as cured and one who subsequently had a perforation. Johns and Grose⁸ in forty-one carefully followed patients had seven unsatisfactory results: three from ulcer recurrence and four from gastric retention. Four of their patients required re-operation (although in three no obstruction was found) and two had subsequent hemorrhage. Of their seven failures, four obtained eventual relief from gastroenterostomy but two did not. In the total series they obtained unsatisfactory results in 17 per cent (27 per cent of those having had vagotomy alone). Thirteen of Moore's⁹ 116 patients developed a recurrence, eleven of them eventually recovering on a medical program and only one requiring subsequent subtotal gastric resection. Wilkinson and Sullivan,¹⁰ in parallel series, respectively, with gastrectomy alone and with gastrectomy plus vagotomy, found an equal recurrence rate but slightly better satisfaction on the part of the patient when only gastrectomy was done.

Medical management of the refractory peptic ulcer patient is admittedly unsatisfactory. To date the most consistently good results have followed subtotal gastrectomy. Although in some instances secondary ulceration, anemia or a nutritional disturbance follow, the effects of extensive gastrectomy in the previously unoperated patient have been satisfactory, both immediately and ultimately, in 85 to 95 per cent of the cases. They have been best when

⁵ VANSANT, F. R. Late effect of section of vagus nerves on gastric acidity. *Proc. Staff Meet., Mayo Clin.* 6: 576, 1931.

⁶ GRIMSON, K. S. Clinical evaluation of complications observed after transthoracic vagotomy. *Arch. Surg.*, 55: 175, 1947.

⁷ WALTERS, W. Gastric neurectomy. *Arch. Surg.*, 55: 151, 1947.

⁸ JOHNS, T. N. P. and GROSE, W. E. Symposium on vagotomy in peptic ulcer: early surgical results in forty-three cases. *Bull. Johns Hopkins Hosp.*, 81: 92, 1947.

⁹ MOORE, F. O. Follow-up of vagotomy in duodenal ulcer. *Gastroenterology*, 11: 442, 1948.

¹⁰ WILKINSON, S. A. and SULLIVAN, J. C. Vagotomy combined with subtotal gastrectomy. *Gastroenterology*, 11: 457, 1948.

gastrectomy was done for gastric ulcer and worst when done on psychoneurotic patients with duodenal ulcers. Such results, therefore, may be regarded as a basis for comparison with those eventually obtained from vagotomy.

It may now be said that the immediate results of vagotomy are hardly so satisfactory as those of gastric resection. The relief of pain that usually results from vagotomy may in itself lead to a false sense of security, since in several instances it has masked a perforation. The depression of gastric motor function often accounts for a prolonged period of epigastric fullness and vomiting even when gastro-enterostomy also has been performed. As yet no assurance can be given that the previous gastric acidity will not recur. The ultimate effect of the operation on the pancreatic secretion is still in doubt. Secondary or associated gastric surgery is frequently necessary and, as is fully appreciated, when a stomal ulcer once develops (as it may after gastro-enterostomy) its management, even by

gastrectomy, leads to poor results. At any rate, vagotomy alone is usually contraindicated in gastric ulcer because of the difficulty in ruling out a malignant lesion.

On the other hand, vagotomy does seem to have found a place in the management of the marginal ulcer in which the other current operations often fail. Also it may be found useful in the psychoneurotic patient with a duodenal ulcer in whom gastrectomy now gives its poorest results. Indeed in the latter instance it may constitute a rational procedure because of the probability that in such a patient the mechanism of ulcer production depends primarily on a disturbance of the autonomic nervous system. Its place in the management of the ordinary duodenal ulcer patient, however, has not as yet been determined and, until further observations have been made on the patients already vagotomized, it would seem wise to exercise great caution in subjecting more patients with this type of ulcer to the operation.

T. GRIER MILLER, M.D.

Intubation Studies in Intestinal Allergy*

EUGENE M. SCHLOSS, M.D.

Philadelphia, Pennsylvania

IN the investigation of gastrointestinal allergy the principal modalities up to this time have involved a great variety of procedures including (1) methods of skin testing (scratch, intradermal and patch tests) for the presence of reagents; (2) clinical observations incident upon the use of elimination diets and, as a special adaptation of this method, the pulse rate study of Coca; (3) roentgenologic study of the effect of barium-specific food mixtures upon the tonus, motility and pattern of the several segments of the alimentary canal; (4) direct observation of local changes due to allergenic substances as seen through the gastroscope or anoscope and (5) evaluation of alterations in the hematologic pattern, such as leukopenia, eosinophilia, etc., at certain intervals after the ingestion of suspected foods. Of these methods those dealing with skin testing are probably the least accurate; there is a notably high incidence of false reactions, both positive and negative;¹ in fact, the existence of a true reaction in the skin is a matter of conjecture except in those instances in which urticaria is the clinical manifestation of specific food sensitivity.

From the standpoint of practical demonstration, elimination diets, as advocated by Rowe¹ and others,^{2,3} hold a deservedly high place in the management of the food-sensitive patient; such a method of investigation requires time, patience and accuracy of judgment on the part of the clinician but frequently focuses direct attention upon the offending substances. X-ray studies in this field began in 1915 when Crispin⁴ first observed the appearance of angioneurotic edema of the pylorus roentgenologically. Two years later Christian⁵ reported two

instances of probable digestive tract allergy in which abdominal pain and radiologic findings had led to laparotomy for gross organic disease. In 1921 Duke⁶ first described roentgenographic appearances of the stomach in a specific food sensitivity, and subsequently Eyermann,⁷ Rowe,⁸ Andresen,⁹ Fries and his associates^{10,11} and others have contributed to the study of such changes in all segments of the alimentary tube. This method has been brought to such a stage of development that, in the opinion of the author, it may serve as a point of reference to which the results of other types of investigation may be directed for confirmation; when, for example, elimination diets have apparently singled out a specific food sensitivity, the diagnosis may be substantiated by the performance of a gastrointestinal x-ray series, using first the usual barium suspension as a control, to be followed by the incorporation of a sample of the suspected food allergen with the barium mixture. Such studies have not gone unchallenged; Pendergrass and his associates,¹² Ravdin,¹³ Fantus,¹⁴ Macy¹⁵ and others have demonstrated changes in the small bowel pattern and motility on the addition of various substances, including 50 per cent glucose solution, egg white, olive oil, milk, bran and other nutritive elements, to barium suspensions. However, these alterations do not appear to be of the same order of divergence from the normal as do those marked changes observed in the individual who presents evidence of true food sensitivity and who usually exhibits the subjective and/or objective manifestations of his sensitivity during the performance of the study although he may be unaware of

* From The Jewish Hospital, Philadelphia, Pa.

administration of the allergen. In their study of gastrointestinal allergy in children in 1943, Fries and Mogil described radiologic changes which they concluded were "effects due to allergenicity of food and not to its nutritive content" inasmuch as subjects who had lost their sensitivity to specific foods presented normal roentgenograms when retested with the same barium food mixtures. In 1941 Thomas and Renshaw¹⁶ brought attention to the method of direct proctoscopic observation of the reaction produced by contact of an allergen with the rectal mucosa and found erythema, edema, vascular engorgement and hemorrhage in varying degrees. Similar mucosal effects in the stomach have been reported by gastroscopic observation after oral administration of suspected allergenic substances. The considerable literature regarding leukopenic and eosinophilic phenomena has represented another aspect of the search for knowledge concerning digestive allergy; the original observations by Rinkel¹⁷ and Vaughan¹⁸ have recently undergone revision and elaboration by Randolph¹⁹ which further enhances the value of studies in the investigation of individual patients.

To these methods it is now proposed to add a new type of investigation. This is the employment of a balloon-tipped, double lumen intestinal tube by means of which numerous phenomena may be studied from kymographic recordings. By this method it is possible to observe the degree of tonus and the rate of motility in a selected segment of the intestine and the changes in these functions occasioned by the oral or tubal introduction of suspected food allergens. The reaction interval and duration may be determined and the effect of therapeutic agents may be evaluated *in vivo*.

METHOD

The device employed in this study is illustrated in Figure 1. It consists of a Miller-Abbott tube, the suction lumen of which is clamped off except for the removal of intestinal secretions or the introduction of selected foods, indifferent control agents

or pharmacologic products. The other lumen, capped at its distal terminus by the balloon, is connected proximally to a closed, diaphragm-capped chamber in such a manner that pressure changes in the chamber may be communicated to an

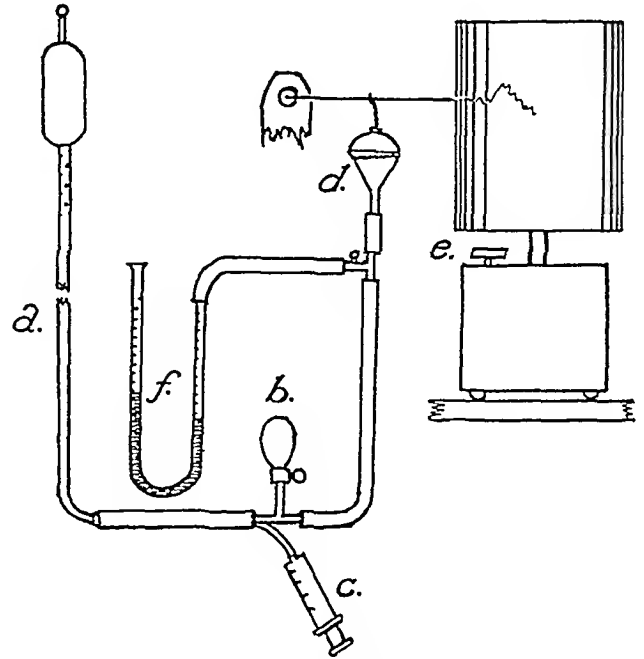


FIG. 1. Apparatus for procedure: (a) Miller-Abbott tube; (b) bulb for inflation of balloon-diaphragm system; (c) syringe for instillation of test substances; (d) pressure chamber-diaphragm unit; (e) electrically driven, timed kymograph; (f) water manometer.

accurately timed electrically-driven kymograph; a T-tube inserted into this system is attached to a water manometer in order to record pressure changes in cc. of water, and to correlate these measurable changes with alterations of amplitude on the kymographic recording. In order to obtain some measure of uniformity in the present study all observations have been made after implantation of the balloon in the jejunum, approximately opposite the ligament of Treitz, as observed fluoroscopically. Routinely after passage of the tube into the duodenum sufficient air was introduced into the balloon to record a manometric pressure of 10 cc. of water. This was done both to facilitate passage of the tube into the jejunum and to provide an easily compressible surface against which the wall and contents of the intestine might exert pressure. Once the balloon was found to be situated in the desired segment, kymographic recordings

were made during the "resting" phase of small intestinal activity and after the introduction, singly, at intervals of not less than twenty minutes, of various control and suspected food substances in liquid or suspended form.

In 1939 Wangenstein,²⁰ measuring the intraluminal pressure of isolated loops of small intestine during the course of a surgical operation for intestinal obstruction, reported pressures of 4 to 14 cc. of water. One year later Brody and his co-workers²¹ clearly described the characteristic rhythmic contractions and tonus alterations of the stomach and small bowel. In 1943 Abbott and his associates²² made a study of intraluminal pressures in various segments of the digestive canal, using their well contrived "pressure capsule" to detect alterations which might then be transmitted to an automatic recording system. As a result of parallel observations employing both the pressure capsule and the balloon technics Abbott pointed out the superiority of the pressure capsule method, stating that "the balloon record, which in a rough way is a measure of the capacity of the gut lumen over a limited area, shows a pattern of far greater variability, indicating that not every contraction or relaxation of the intestinal musculature brings about an appreciable change in intraluminal pressure." However, as a matter of availability and cost of apparatus, the balloon method was chosen for the study on which this report is based, and the basic and phasic changes in pressure in normal individuals have been found to parallel closely those observed by Abbott's group.

RESULTS

In normal individuals tracings by means of this procedure have exhibited the rhythmic contractions and tonus alterations which have been reported by previous workers. A typical normal kymographic recording is illustrated in Figure 2. Due to the initial introduction of sufficient air to produce a manometric pressure of 10 cc. of water, measurement of the basal pressure

cannot be performed accurately in all cases inasmuch as some diastolic pressure readings must lie below that level. The phasic pressure changes in twenty normal patients have been found to reach a maximum of 12 to 38 cc. of water spontaneously or after the intraluminal instillation of water, 10 per cent glucose solution or liquid foods to which no specific sensitivity has been known or suspected. These foods have included beef extract, wheat extract, tomato juice, fruit juices, milk, etc. In these normal individuals the rhythmic pressure changes occasioned by introduction of such substances rise above that recorded in a basal period but do not rise beyond those found spontaneously in other normal subjects nor in the same subjects at other times. The frequency of the phasic waves is usually increased immediately after introduction of such substances, but after periods of forty seconds to three minutes this heightened effect subsides and the fasting rhythm is resumed. This probably represents the time interval necessary for the local bowel segment to accustom itself to the distending effect of the 10 cc. quantities of fluid introduced or may represent the time necessary to propel the liquid beyond the space occupied by the balloon. While it is readily admitted that this method of observation cannot be used for the precise measurement of intraluminal pressures, relative constancy of the phasic pressure changes so observed does permit its use as a control agent against which more violent reactions might be contrasted if found to occur.

In cases of intestinal food allergy the tracings secured prior to introduction of allergenic foods have shown no divergence from the range of variability found in non-allergic individuals. The frequency of contractions, rhythmicity, duration and amplitude of phasic pressure waves have been quite comparable throughout. In this group, after the position of the tube has been verified fluoroscopically and the initial pattern has been inscribed, a series of indifferent or non-suspect elements is introduced through the tube routinely; these

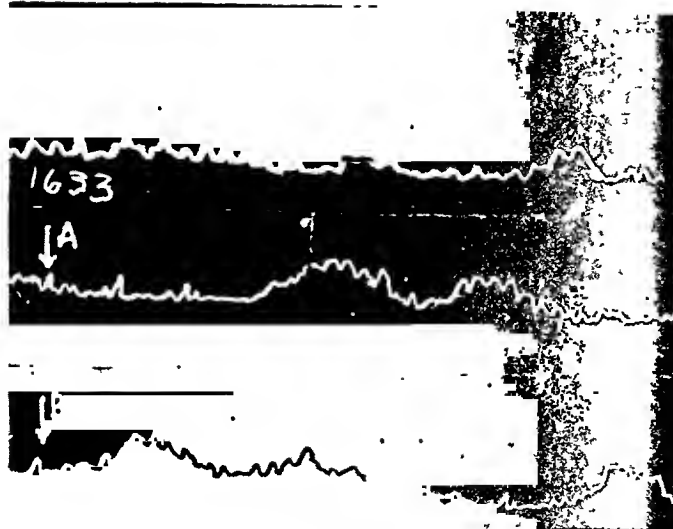


FIG. 2

FIG. 2. Normal tracing. Upper line demonstrates continuous fluctuations in intraluminal pressure; at point A 10 cc. of 10 per cent glucose was introduced and stimulated phasic pressure waves in forty-five seconds; twenty minutes later an almost identical pattern of phasic pressure waves was recorded spontaneously in line B. Manometric pressure in each line did not exceed 28 cc. of water.

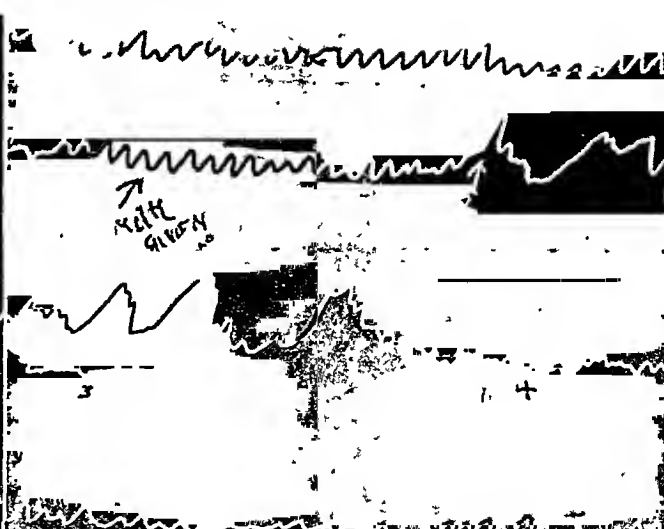


FIG. 3

FIG. 3. Case 1, milk allergy. Tracing illustrates abnormal intraluminal pressure changes following instillation of 10 cc. of milk, the initial severe contraction occurring in two minutes, with a return to the "resting" level in four minutes. Peak manometric reading was 78 cc. water.

have included 10 to 30 cc. portions of 10 per cent glucose solution, olive oil, milk, powdered egg suspensions, beef extract and water-thinned purees of a variety of common foodstuffs. Just as in the non-allergic subjects the instillation of simple nutritive elements in small quantities produces transient changes of amplitude and frequency of the phasic pressure waves, which still fall within the limits noted spontaneously in normal subjects or in the same individuals at other times without the introduction of anything by tube. This control period is followed by the instillation of 10 cc. quantities of foodstuffs which, by reason of history, elimination diets or prior x-ray study, are suspect. The nature of each test substance is, of course, concealed from the patient throughout the period of observation in all cases.

Following the instillation of foods allergenic to a given individual, the alterations in the kymographic tracings have been notable. Furthermore, these alterations, usually violent, have frequently been accompanied by the subjective manifestations of which the patient had previously complained. The interval between the contact of the allergenic food with the

jejunal mucosa and the onset of abnormal kymographic phenomena has varied from two to twelve minutes in this series, with a mean of four minutes. The onset of the reaction phase is marked by a rather gradual increase in the height and duration of the phasic pressure waves. At times, as illustrated in Figure 8, the individual waves increase rapidly in acuity and amplitude and the interval between successive contractions decreases progressively until a maximum point of activity, after which there is a gradual recession in reverse sequence. In other cases there is superimposed upon more moderately accentuated phasic pressure waves a series of acute spiking inscriptions of varying amplitude, all marked by their extreme height as compared with any change in the underlying basic rhythm; Figure 3 represents an example of this type. The total duration of the reaction to a given allergen varies from two to eighteen minutes with, in this series, one instance in which the violence of the reaction culminated in regurgitation of the entire tube. There does not appear to be any constant relation between the duration of the reactive phase and the severity of the contractions as measured either in fre-

quency or in amplitude. In the present series of twenty-two cases a wide variety of combinations has been secured. In all cases, regardless of the type of configuration recorded, the manometric pressures have well exceeded the highest readings found in non-allergic reactions. These have varied from 56 cc. of water, well above normal readings, up to 152 cc. of water, a reading obtained during a particularly violent subjective reaction of intense cramping pain. The range of manometric pressures observed in the allergic patients is thus seen to be sufficiently removed from the 12 to 38 cc. readings during control tests to be significant. This factor, combined with the coincident appearance of altered kymographic patterns of localized intraluminal pressure changes, seems to enhance the specificity of the study. Once the reactive phase characteristic of that particular jejunal segment has subsided, the kymographic pattern returns to its pretest level although the patient may continue to evidence further symptomatology as more distal areas are successively involved for variable periods of time; in other instances the subjective manifestations subside with return of the tracing to resting levels, as though the reactive mechanism had been exhausted or the allergenic substance itself had been, in a manner of speaking, neutralized. In a few instances a second instillation of the known allergen has been performed after various intervals of time during the course of the same intubation, but this group of observations is as yet too small to permit deductions or conclusions. In a single instance, Case I, the tracing was marked by a rhythmic pattern due to respiratory movement; this isolated case presented unusual postoperative tension of the abdominal wall.

The data and tracings from two of the confirmed cases of gastrointestinal food allergy studied by this method to date will serve to illustrate the foregoing observations. Their presentation is detailed for the dual purpose of describing the mode of application of the procedure and of emphasizing

the confused and obscure clinical patterns which characterize so many instances of gastrointestinal food allergy.

CASE REPORTS

CASE I. M. A., a female aged forty-seven years, presented a lengthy history of digestive disturbances beginning with abdominal cramps and constipation in childhood, requiring constant medical attention. In 1941 she developed epigastric fullness and distress about one hour after meals; after a few months symptoms abated, recurring thereafter irregularly. In 1945 the symptoms became severe and in early 1946 her first gastrointestinal x-ray series disclosed an ulcer on the lesser curvature of the stomach. On a modified Sippy regimen her response was unsatisfactory and in the fall of 1946 the position and nature of the lesion was confirmed gastroscopically. However, when treatment was intensified, anorexia, nausea and vomiting occurred although there was no evidence of any obstructive phenomena. On December 2, 1946, total gastrectomy with esophagealjejunal anastomosis was performed. Examination of the resected tissues disclosed "chronic ulcer of the stomach; chronic lymphadenitis"; no evidence of malignancy was found. The ulcer was 2 cm. in diameter, mid-way between the cardia and pylorus on the lesser curvature, was firm and indurated and extended to within 2 mm. of the serosa. Convalescence was stormy. Appetite failed to return and various modifications of the ulcer diet failed to alleviate the high abdominal pain, nausea and vomiting; weight, formerly about 120 pounds, had dropped to 106 pounds preoperatively and 88 pounds on hospital discharge. Despite supplementary proteolysates, frequent feedings according to the Sippy regimen, crude liver extract and various forms of therapy, the weight was still at the level when the patient was first seen on April 25, 1947. Watery, explosive stools had occurred after most feedings, three to six times daily since the time of operation, but none had contained gross blood and none had been tarry.

The patient appeared ill and emaciated. The abdomen was scaphoid and extremely thin-walled; peristaltic movements were readily observable as rapid and forceful and, at times, were accompanied by visible expressions of pain. There was questionable high epigastric tenderness. Blood count showed a borderline anemia;

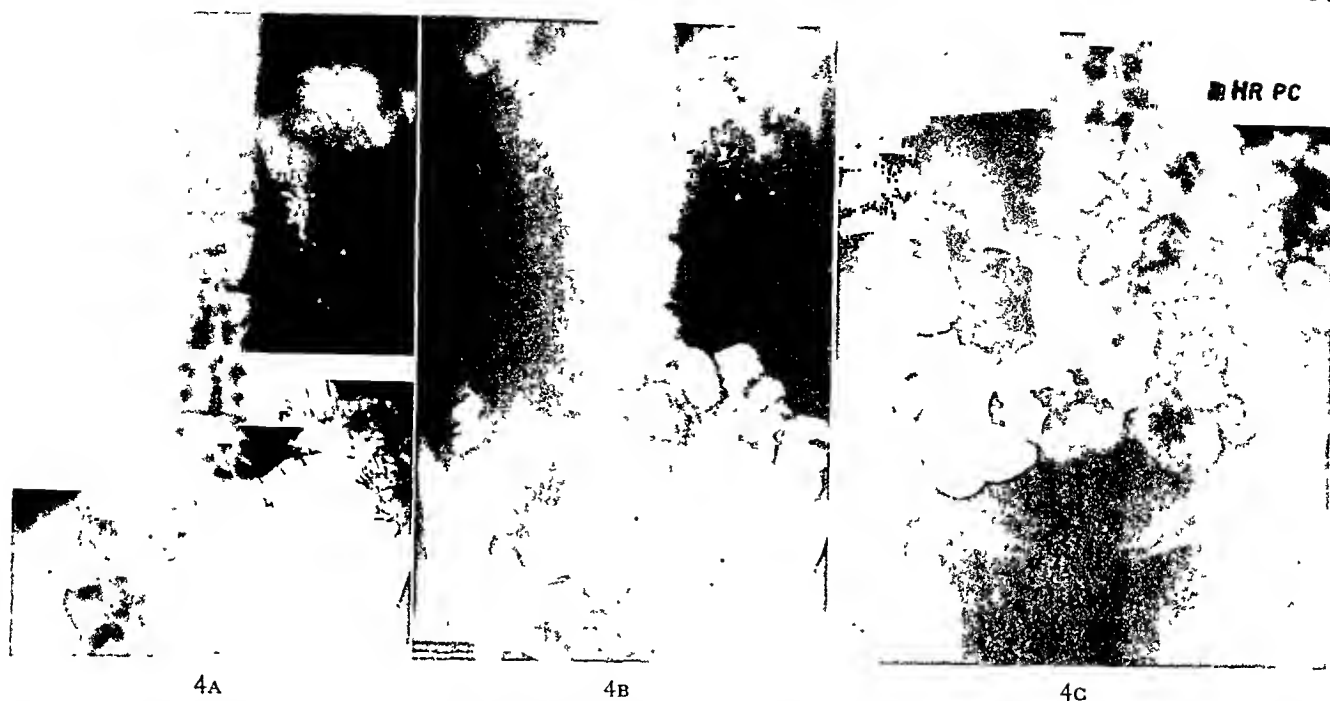


FIG. 4. A, x-ray four and one-half hours after plain barium meal; motility was delayed but the pattern was normal; B, three-quarters of an hour after introduction of milk the pattern was distorted by segmentation, pooling and narrowing or dilatation of the loops; C, one hour after milk there were similar but more advanced alterations.

sedimentation rate was normal; stool examinations were negative for occult blood and were abnormal only in containing some undigested starch granules.

Partly because of the poor physical condition of the patient and partly because the possibility of food allergy had been obscured by the organic nature of the pre-existing disorder, intubation study was not made until September 26, 1947. Figure 3 represents the tracing made on that date. The tube was readily introduced orally, passed through the jejunal stoma and on to a position opposite the ligament of Treitz. A control instillation of 30 cc. of 10 per cent glucose solution failed to alter the tone or to make any alteration of the strong intercurrent respiratory rhythm which was caused by the contracted abdominal wall. However, two minutes after instillation of 10 cc. of milk, marked irregular contractions appeared, produced sharply abnormal phasic pressure changes and were reflected in the patient's complaint of cramps and nausea. The duration of the reaction was two minutes, after which the inscription resumed its former pattern; however, the patient's crampy pain persisted and was relieved only after passage of a watery stool about twenty minutes later. On October 2, 1947, roentgenologic studies,* illustrated in Figure 4,

were reported as follows: "Initially the jejunum and proximal ileum fill very rapidly and present an entirely normal pattern. Between 15 minutes and three hours, however, there is very little further progress of the meal. Fluoroscopy was done in three hours but no film was taken. Even at four and a half hours the meal has not reached the cecum but the pattern still remains normal. After the four and a half hour film, the patient was given a glass of milk and films were taken in three quarters of an hour and one hour. These show very definite change in the appearance of the small bowel. Motility is increased so that the barium mixture passes into the cecum. The normal pattern is disturbed and there is segmentation, pooling and areas of narrowing and dilatation. In the terminal ileum the lumen is so reduced that it suggests the string sign seen in regional enteritis. This does not appear to be constant and is probably due to spasm rather than organic change."

Since studies had thus clearly demonstrated an intestinal milk allergy, a new phase of therapy was instituted. At first desensitization with milk propeptans was attempted according to the method described by Urbach²³ and while the patient was partially relieved, some abdominal burning and distress continued to appear about fifteen minutes after feedings, lasted for one hour and then disappeared until the next feeding. After two weeks a second intubation study was performed, the tracing of which is repre-

* Roentgenologic studies embodied in this report were performed by Harold J. Isard, M.D. and William Serber, M.D., Philadelphia, Pa.

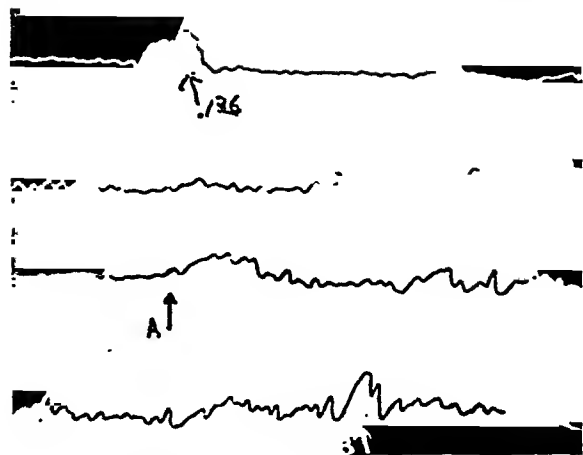


FIG. 5. Following treatment with milk propeptan, of which two capsules were given forty-five minutes prior to instillation of 10 cc. of milk. The arrow at 1:26 marks artefact produced by sneezing. A, beginning reaction occurring six minutes after milk; B, last abnormal pressure change seven minutes later.

sented in Figure 5. Forty-five minutes after swallowing two capsules of milk propeptan, 10 cc. of milk was instilled. Six minutes later the patient complained of discomfort and almost immediately thereafter the basic tonus level rose and phasic pressure waves showed marked accentuation for a period of seven minutes, culminating in a sharply severe crampy pain at the height of one spastic phase. Thereafter the tracing reverted to its former status.

A few days later, after abstinence from milk and milk products, the administration of thephorin (phenindamine, Roche) 25 mg. twice daily was begun, and milk was permitted in small amounts throughout the day, increasing to a total of 1 pint daily. During the six months since this change in therapy, diarrhea and abdominal cramps have occurred in widely separated isolated episodes. Gradual improvement in weight and nutrition have occurred. The dosage of thephorin has been established at 25 mg. once daily although the daily intake of milk is divided into several small feedings. A tracing taken on December 16, 1947, is recorded in Figure 6; after the instillation of 50 cc. of milk it shows no significant aberration from the resting pattern for this patient.

CASE II. H. L., a male aged forty-four years, had recurrent attacks of right lower quadrant pain beginning in 1915, at the age of twelve years. Two years later appendectomy was performed and he was free of digestive symptoms until 1921 when he developed pain in the right upper quadrant, with radiation to the right

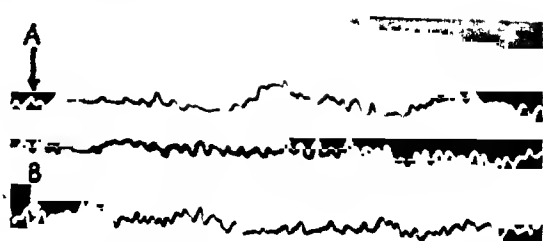


FIG. 6. Tracing made after treatment with phenindamine. A, introduction of 10 cc. of 10 per cent glucose solution followed by phasic pressure waves, the peak reaching a manometric reading of 22 cc. of water. r, instillation of 50 cc. of milk followed by no significant alteration from the resting phasic in the middle inscription.

subscapular area, constipation and heartburn. Symptoms continued intermittently and in varying degrees of severity until 1925, at which time a clinical diagnosis of duodenal ulcer was made and x-rays were reported as "suggestive of atypical ulcer." An ulcer diet was poorly tolerated and the syndrome remained active. During the next five years gastro-enterologic and radiologic opinions leaned toward peptic ulcer plus gallbladder disease but appropriate therapeutics did not effect consistent improvement. In 1930 the patient discovered his own untoward reaction to certain foods, notably milk, malt products, lima beans, peas and chocolate, and in 1935 x-ray disclosed a normal upper digestive canal and gallbladder but generalized colonic spasticity. During the following nine years there were three attacks of "food poisoning," consisting of nausea, vomiting and diarrhea of twenty-four hours' duration: following the acute phase of the last such attack, there was anorexia and simple diarrhea for about six months. At that time the stools were found to contain ova of *Endamoeba histolytica* and appropriate therapy effected a cure. However, stools continued to be soft, and in 1941 another gastro-enterologist first suggested the possibility that an allergic state might have been responsible for the original symptom complex or might represent an acquired sensitivity. In 1945, about three hours after a meal which included clams, the patient suffered vise-like high epigastric pain of sudden onset, became pale, sweaty and weak; the pulse rate was accelerated and the upper abdomen became rigid. An acute coronary episode was suspected but after seven hours the pain had shifted to the right upper quadrant, with right subscapular radiation. Ensuing studies, including electrocardiogram, cholecystography and

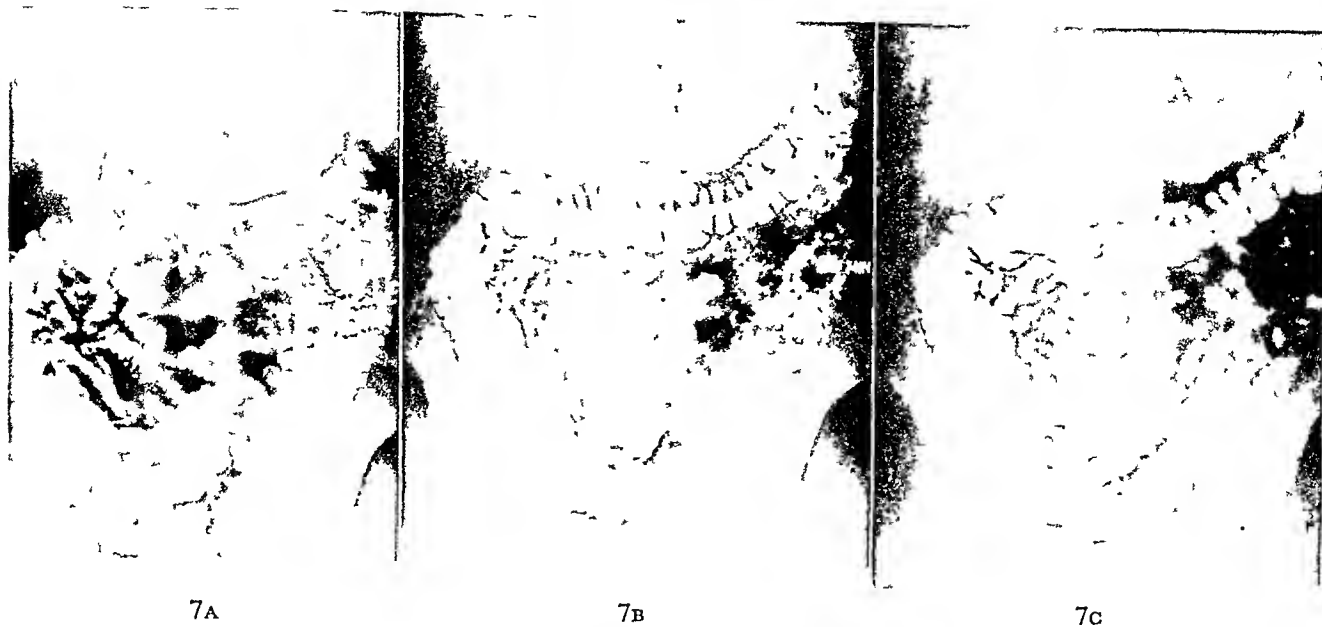


FIG. 7. Case II, A, x-ray seventy-five minutes after administration of plain barium meal; there was a normal small intestinal pattern with a continuous stream of barium from the stomach to the terminal ileum; B, thirty minutes after ingestion of clams: there were segmentation of the loops, a suggestion of coarsened mucosal folds, hypertonicity and irregularity of the caliber; the head of the column at the splenic flexure; C, thirty minutes later there was no progress or change.

sigmoidoscopy, were negative. A bland diet was instituted, but diarrhea continued intermittently.

When this patient was first seen in August, 1947, physical examination revealed nothing of significance. Blood count, sedimentation rate and stool examinations were entirely normal. Biliary drainage resulted in the delivery of a well concentrated specimen which was normal on microscopic examination. Sigmoidoscopy and examination of direct smears from the sigmoid and rectum were negative. Stool cultures disclosed only predominant coliform organisms. Electrocardiography and cardiac consultation indicated no evidence of cardiovascular disease.

On October 9, 1947, roentgenologic studies were reported as demonstrating normal esophagus, stomach and duodenum and normal colon except for some irritability and spasticity of the cecum and proximal ascending colon; the mucosal pattern appeared entirely normal. With regard to the jejunum and ileum, the radiologists reported: "The calibre of the jejunal loops is normal throughout and the mucosal pattern is of the normal feathery type. Progression through the small bowel is quite rapid and at the end of 30 minutes the head of the meal has reached the terminal ileum. The film at this time discloses a continuous stream of barium from the stomach to the terminal ileum. Despite the rapid transit through the small bowel, there does not appear to be too rapid emptying of the stomach. The coils of the ileum appear normal

and there is no undue hypertonicity or segmentation. Seventy-five minutes after administration of the barium meal there is again no evidence of segmentation or undue hypertonicity. At this time the patient was given six clams. A film exposed thirty minutes later discloses a marked change in the appearance of the small bowel pattern. There is hypertonicity of many of the loops, the lumens of which are irregular in calibre; segmentation is apparent and there is a suggestion of some coarsening of mucosal folds. The head of the barium meal has progressed to the splenic flexure. The next film was exposed 60 minutes after the meal and the appearance remains quite comparable to that noted on the 30-minute film." Figure 7 demonstrates the significant plates in this case.

It was not until January, 1948 that an opportunity arose for intubation study, a kymographic recording of which is represented in Figure 8. After negative trial instillations of 10 cc. quantities of milk and of lamb extractives, 10 cc. of fresh clam juice was passed into the jejunum. Two minutes later an initial severe contraction was recorded coincidentally with the patient's complaint of high epigastric pain. This was followed in eighty seconds by a stronger wave of hypertonus and thereafter by a succession of strong contractions which progressively increased in frequency, acuity and amplitude as recorded on the kymograph; this soon mounted to a six-second interval between subjectively

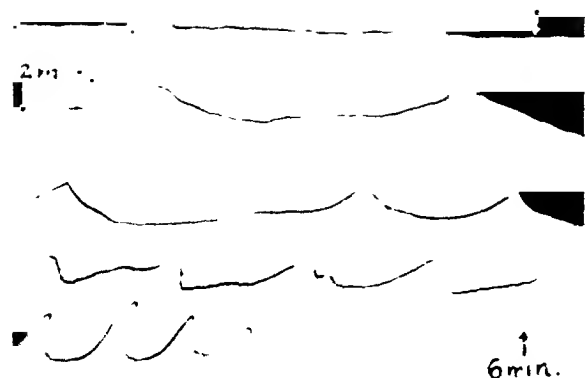


FIG. 8. Sections from tracing illustrate a progressive increase in acuity, amplitude and frequency of exaggerated pressure changes in response to allergenic food. Clam juice, 10 cc., was instilled at the point marked by the upper arrow. There was an initial severe contraction in two minutes, followed by rapid progression culminating in regurgitation of the tube in six minutes.

painful contractions which eventuated in violent retching and regurgitation of the tube.

Since the date of this study, elimination of clams and other offending foods from the patient's dietary has resulted in marked amelioration of digestive tract symptoms.

COMMENTS

The difficulties attending the diagnosis of gastrointestinal food allergy are notorious; they have received comment from Duke,²⁴ Moore²⁵ and almost every other investigator in this field. It has been stated repeatedly that food allergy can mimic, in part or in whole, almost any gastrointestinal disease; the manifestations depend upon the segment of the alimentary tract in which the reaction occurs and upon the qualitative nature and quantitative extent of the reaction. Any portion of the digestive tube may be the site of an allergic reaction. Thus Fries and his co-workers found x-ray evidence of gastric reactions in children in whom subjective symptoms appeared promptly after ingestion of allergenic foods; Hampton and Cooke²⁶ reported abnormal segmentation of the small intestine in cases of delayed type of food allergic reaction; many x-ray studies have disclosed colonic abnormalities following oral administration of food allergens, and the proctoscopic observations of Thomas

and Renshaw have implicated directly the mucosa of that segment of the canal. The present intubation studies not only confirm the susceptibility of the jejunum but also suggest that gastric digestion fails to denature the foods thus far used in this study in such a manner as to destroy their allergenicity. At this point it will be recalled that in Case II, clams appeared to elicit similar small bowel responses when given by mouth in the roentgenologic study and when introduced directly into the jejunum by tubal instillation. This has been demonstrated in other cases with egg, wheat and milk. Thus it would seem that without regard to the precise chemical or hormonal reaction which mediates the local response, there are food-specific allergens which are capable of initiating certain phenomena within two minutes of the time they come into contact with the jejunal mucosa and which are not sufficiently altered by gastric digestion to prevent these effects. The question of whether the minimum interval of two minutes represents the period necessary for local tissue reaction, absorption, hormonal elaboration, neural intervention or any combination of these modalities remains unanswered at this time.

In this study, after passage of the tube into the duodenum, sufficient air was introduced routinely into the balloon to record a manometric pressure of 10 cc. of water. It is readily seen that this would preclude the possibility of accurate measurement of basic intraluminal pressure. Yet, as previously mentioned, phasic pressure changes of 12 to 38 cc. of water were obtained during "resting" periods and following the introduction of non-allergenic liquid foodstuffs. In view of the presence of the balloon-air mass these phasic pressures would seem to represent (1) the rhythmic contractions characteristic of the constant activity of the small intestine, (2) the force of intestinal muscular contraction elicited as a simple response to the distending effect of the balloon, (3) the force produced by peristaltic waves attempting forward propulsion of the balloon itself or of liquid past the

partial obstruction produced by the balloon or (4) at times, a summation of those factors.

The studies of Posey and his group,²⁷ using a balloon technic in ileostomized humans, have clearly demonstrated three configurations of small intestinal activity, of which one is a constant series of rapid, rhythmic contractions, another of larger, slower contractions which are sometimes propulsive and a third which is produced by tonus waves on which the other types are superimposed; when propulsion occurs in the third type, it is invariably associated with superimposition of the second type of wave. Attempts at propulsion are thus seen to be characterized by considerable augmentation of intraluminal pressure. This is still, however, within observed normal limits. In the experiments by Abbott in which water was injected proximal to a distended balloon in sufficient amount to simulate the intraluminal distention occurring in acute artificial intestinal obstruction the phasic pressures rose only as high as 50 cc. of water.

On the other hand, after the introduction of an allergenic food the components making up the total reaction must include those normally present plus elements peculiar to the intestinal allergic reaction. Those elements, according to roentgenologic, gastroscopic and pathologic evidence, consist of local mucosal edema and increased muscle tonus, at times exaggerated to high degrees of swelling and spasticity. It is probable that both these elements play a role in production of the kymographic records in this study. Local edema may well serve further to occlude the jejunal lumen at and proximal to the site of the balloon, at least to a degree at which both regular phasic and interjected stronger muscle contractions are more sharply communicated to the kymographic tracings. The studies made by Wing and Smith²⁸ on sensitized guinea pigs showed no alteration in small bowel pattern even when the animals were in fatal anaphylactic shock; in these experiments it seems probable that the intestinal wall did not assume the function of shock organ.

However, in commenting on that presentation, Gray referred to the studies by Gray, Harten and Waltzer^{29,30} of the gross and histologic allergic reactions in rhesus monkeys and concluded that the spastic phenomena were secondary to the tremendous edema of the mucous membrane at the site of the reaction. While it is likely that local edema is an early and marked intestinal mucosal reaction to the presence of an allergen, and possible that spastic phenomena are secondary thereto, the wave and spike nature of the inscriptions in the kymographic recordings here obtained seem to represent too dynamic an activity to be the result of edema alone. Rather, they embody characteristics which appear attributable largely to gross exaggeration of normally present phasic changes and to the interjection of strong spastic contractions. The elevation of the entire tracing during an observed period of reaction, slightly above the baseline noted before and after the reactive span, may represent a prolonged increase in basic tonus or the constrictive effect of mucosal edema upon the balloon or, again, a combination of those factors.

On the basis of the results in this study the intubation procedure appears to afford a means of securing confirmation of the specificity of food allergens in a given individual. It may be performed in such a manner as to test a number of foodstuffs during the course of a single intubation, instilling them singly at intervals of twenty minutes since, in our experience, the longest period of reaction latency has been eighteen minutes. Thus far the feasibility of instilling additional trial foods after the subsidence of a typical reaction to an allergenic one has not been determined; this procedure and that of repeating instillation of the same allergenic food after varying intervals of quiescence may afford further insight into the mechanism of food allergy generally. The specificity of the method seems to be equal, if not superior, to that of the radiologic method utilizing food-barium mixtures; however, the radiologic study is

limited to the trial of one or, at most, two foodstuffs during a single period of study. and extension of the procedure to a larger series of suspected foods promotes the risk of overexposure to radiation.

CONCLUSIONS

The intubation procedure is not recommended as a routine method for the discovery of food allergy. At the present time this disorder is most apt to be suspected by carefully detailed case histories. Routine gastrointestinal studies and x-rays then serve to exclude observable organic lesions. Clinical observation, elimination diets and the study of leukocytic phenomena are useful as a screening process for the implication of specific foodstuffs. Finally, roentgenologic study with barium mixed with suspected foods and/or use of the intubation procedure may then be employed to substantiate the diagnosis. This appears to be the optimum point for application of the intubation study in the diagnosis of the individual patient and, as previously indicated, this procedure has certain advantages over the roentgenologic method. In a more general sense, the method as here described, or in greater elaboration, provides an additional method for the investigation of intestinal food allergic phenomena. From a study of the kymographic records thus far obtained there appears to be evidence for the presence of exaggerated phasic motor changes and the interpolation of spastic contractions of the intestinal muscle, both being superimposed upon an elevated intraluminal pressure. This latter may be secondary to local reactive edema, or to reactive increase in tonus or to a summation of these factors

REFERENCES

1. ROWE, A. H. Food Allergy. Its Manifestations, Diagnosis and Treatment, with a General Discussion of Bronchial Asthma. Philadelphia, 1931. Lea and Febiger.
Rowe, A. H. Gastro-intestinal allergy. *J. A. M. A.*, 97: 1440, 1931.
2. COCA, A. T. Familial Nonreactive Food-Allergy. Springfield, Ill., 1945. Charles C. Thomas.
3. RANDOLPH, T. G. Food allergy. *M. Clin. America*, 32: 245, 1946.
4. CRISPIN, E. L. Visceral crises in angioneurotic edema. *Collect. Papers, Mayo Clin. & Mayo Hosp.*, 7: 823, 1915.
5. CHRISTIAN, H. A. Visceral disturbances in patients with cutaneous lesions of the erythema group. *J. A. M. A.*, 69: 325, 1917.
6. DUKE, W. W. Food allergy as a cause of abdominal pain. *Arch. Int. Med.*, 28: 151, 1921.
7. EYERMANN, C. H. X-ray demonstration of colonic reaction in food allergy. *J. Missouri M. A.*, 24: 129, 1927.
8. ROWE, A. H. Roentgen studies of patients with gastro-intestinal allergy. *J. A. M. A.*, 100: 394, 1933.
9. ANDRESEN, A. F. R. Gastro-intestinal manifestations of food allergy. *J. M. Soc. New Jersey*, 31: 402, 1934.
10. FRIES, J. H. and ZIMMER, J. Roentgen studies of children with alimentary disturbances due to food allergy. *Am. J. Dis. Child.*, 54: 1239, 1937.
11. FRIES, J. H. and MOGH, M. Roentgen observations on children with gastrointestinal allergy to foods. *J. Allergy*, 14: 310, 1943.
12. PENDERGRASS, E. P., RAVDIN, I. S., JOHNSTON, C. G. and HODES, P. J. Studies of small intestine: effect of foods and various pathologic states on gastric emptying and small intestinal pattern. *Radiology*, 26: 651, 1936.
13. RAVDIN, I. S. Effect of foodstuffs on the emptying time of the normal and operated stomach and the small intestinal pattern. *Am. J. Roentgenol.*, 35: 306, 1936.
14. FANTUS, B., KOPSTEIN, G. and SCHMIDT, H. Roentgen study of intestinal motility as influenced by bran. *J. A. M. A.*, 114: 404, 1940.
15. MACY, I. G., REYNOLDS, L., SOUTHERS, H. J. and OLSON, M. B. Normal variation in gastrointestinal response of healthy children. *Am. J. Roentgenol.*, 43: 394, 1940.
16. THOMAS, J. W. and RENSCHAW, R. J. F. Proctoscopic observations in gastrointestinal allergy. *Cleveland Clin. Quart.*, 8: 17, 1941.
17. RINKEL, H. J. The leukopenic index in allergic diseases. *J. Allergy*, 7: 356, 1936.
18. VAUGHAN, W. T. Food allergens. III. The leukopenic index; preliminary report. *J. Allergy*, 5: 601, 1934.
19. RANDOLPH, T. G. and RAWING, F. T. A. Blood studies in allergy. V. Variations of total leukocytes following test feeding of foods; an appraisal of the individual food test. *Ann. Allergy*, 4: 163, 1946.
20. WANGENSTEIN, O. H. Experimental and clinical observations relating to the management of acute bowel obstruction. *Ann. Int. Med.*, 13: 987, 1939.
21. BRODY, D. A., WELSH, J. M., MICHAN, I. and QUIGLEY, J. P. Intraluminal pressures of digestive tract, especially pyloric region. *Am. J. Physiol.*, 130: 791, 1940.
22. ABBOTT, W. O., HARTLINE, H. K., HENLEY, J. P., INGERSOLL, T. J., RAYSON, A. J. and ZIEGLER, L. Intubation studies of the human small intestine. XXI. A method for measuring intraluminal pressures and its application to the digestive tract. *J. Clin. Investigation*, 22: 225, 1943.

23. URBACH, E. Diagnosis and treatment of food allergies through propeptans. *Ann. Allergy*, 1: 219, 1943.
24. DUKE, W. W. Allergy as a cause of gastro-intestinal disorder. *South. M. J.*, 24: 363, 1931.
25. MOORE, M. W. Gastrointestinal allergy. *Northwest Med.*, 34: 200, 1935.
26. HAMPTON, S. F. and COOKE, R. A. Protein derivatives as factors in allergy. *Ann. Int. Med.*, 16: 71, 1942.
27. POSEY, E. L., DEARING, W. H., SAUER, W. G., BARGEN, J. A. and CODE, C. F. The recording of intestinal motility. *Proc. Staff Meet., Mayo Clin.*, 23: 297, 1948.
28. WING, W. M. and SMITH, C. A. Spontaneous and induced sensitivity to foodstuffs: x-ray studies of the small intestine in man and guinea pig. *J. Allergy*, 14: 56, 1942.
29. GRAY, I., HARTEN, M. and WALTZER, M. Studies in mucous membrane hypersensitiveness: allergic reaction in passively sensitized mucous membrane of ileum and colon in humans. *Ann. Int. Med.*, 13: 2050, 1940.
30. WALTZER, M. Allergy of abdominal organs. *J. Lab. & Clin. Med.*, 26: 1867, 1941.

I. Motility of the Human Esophagus in Control Subjects and in Patients with Esophageal Disorders*

PHILIP KRAMER, M.D. and FRANZ J. INGELFINGER, M.D.

Boston, Massachusetts

WHEN the human esophagus is studied fluoroscopically after administration of a barium meal, this organ manifests tone (as indicated roughly by the luminal caliber) and phasic activity that comprises three types of waves: primary, secondary and tertiary.¹ The tone and contractions of the human esophagus have, however, been recorded infrequently by the balloon-kymograph technic, and such studies as have been made pertain to strictly physiologic problems.²⁻³ Since balloon-kymograph records of esophageal motility in various clinical conditions were not available, we have used this method in fourteen control subjects without esophageal disorders, in four patients with cardiospasm, in four with scleroderma and in two with mechanical obstruction of the esophagus.

The technic used was that described by Ingelfinger and Abbott,⁴ with the minor modification that the Miller-Abbott tube connecting the esophageal balloon to the recording device was only 100 cm. long. In this system a relatively constant pressure (20 to 25 cm. of water) forces air into the balloon until the resistance of the esophageal wall permits no further inflow. The volume of the balloon therefore indicates the resistance of the esophagus to a distending force and may be considered an expression of esophageal tone. When the volume fluctuates because of phasic activity, tone is calculated as the mean volume of air contained in the balloon between the extremes of phasic contraction and relaxation.

Records were obtained by two procedures: The balloon was allowed either to progress down the esophagus with peristaltic activity or was maintained in one of three standard positions by fastening the tube at the nose. The standard positions, which were invariably ascertained by fluoroscopic means, comprised: (1) upper esophagus--balloon situated behind the manubrium sterni and extending upward into the suprasternal notch; (2) mid-esophagus--balloon at the pulmonary hila; (3) lower esophagus--distal end of the balloon just above the diaphragm. The motility recorded under these conditions is initiated by the presence of the balloon. Except as indicated, the subjects were asked not to swallow. Frequently, however, a subject might swallow involuntarily because of the irritation caused by the presence of the balloon in the esophagus or by the tugging of the tube in the nasopharynx. It is apparent that our records, obtained by stimulating the esophagus with a large, pliable but non-fluid bolus, can be compared only in general terms with motility studies obtained by other means.

CONTROL SUBJECTS

When the balloon was inflated in the upper esophagus and allowed to progress with peristaltic activity, an average of 8" seconds was required before the balloon entered the stomach. Repeated determination of the esophageal transit time in the

* From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

same subject yielded results that were consistent in some but not in all individuals. The variation in transit times in different subjects was considerable, extending from fifteen seconds to five minutes and forty-five seconds. The significance of these transit

stomach may at any moment be recording simultaneously from more than one area of the esophagus and may occupy, as it passes through the cardia, a partially intra-gastric position. For these reasons we believe that the position of the balloon should be

TABLE I
ESOPHAGEAL MOTILITY IN CONTROL SUBJECTS

Subject	Diagnosis	Tone (cc. of air in balloon)			Height of Wave (cc. of air expelled from balloon)			Frequency (No. of waves per minute)		
		Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower
A. S.	Constipation	6	8	7	4-12	14	8-9	9	6	10
O. F.	Functional gastrointestinal disorder	17	12	11	0	7-11	6-8	0	6	6
A. S.	Hypertension	17	11	11	3	4-9	3-9	15	11	12
J. C.	Functional gastrointestinal disorder	10	10	5	4-6	15	3-8	11	6	12
A. M.	No disease	15	12	12	3	21	12	12	4½	6½
F. J. I.	No disease	18	23	24	7-10	17-29	13-19	7	6	6½
F. J. I.	No disease	23	22	6
P. K.	No disease	7	9	7	3-5	9	6	16	6	8
S. L.	Functional gastrointestinal disorder	11	14	11	4-6	19	11	9	5	7
A. S.	Functional gastrointestinal disorder	10	12	4	9-14	7	7
M. M.	Functional gastrointestinal disorder	8	7	7	2-10	12-14	10	7	6	11
W. H.	Cholelithiasis	8	6	6	3	12	10	9	6	6
J. L.	Gastric ulcer	10	14	15	5-8	9-11	10	9	6	6½
N. B.	No disease	9	8	8	3	8-10	10-13	10	8	8
F. S.	Diabetes	10	16	16	13	6	7
Range	7-18	6-23	5-24	2-12	4-29	3-19	0-16	4½-11	6-12
Average	11.3	11.8	10.9	4.5	13.5	9.8	9.5	.65	8.1

times is limited for the esophagus has to propel not only a balloon but an attached tube (weight = 40 Gm.) which encounters variable friction in passing through the nares.

Motility records obtained as the balloon passed down the esophagus were generally unsatisfactory, partly because of the variations in transit time, partly because the exact position of a moving large balloon was difficult to determine. A condom balloon, which measures 5 cm. in length when inflated outside the body, is moulded by the esophagus into a cylinder of smaller diameter but greater length. Because of this length, a balloon travelling toward the

fixed if satisfactory motility records are to be obtained from the human esophagus by our method. On the other hand, Hwang et al.,⁷ who used a quite similar method in dogs, found the motility record obtained as the balloon moved down the esophagus so characteristic that small changes in the wave pattern were considered to be of major significance.

Records obtained by maintaining the balloon in the three standard positions yielded motility patterns that were quite characteristic for each position. In the upper position the wave pattern was irregular and characterized by excursions of small amplitude. By way of contrast, large and

well defined waves succeeded each other in regular sequence when the balloon was inflated and maintained in the mid-position. In the lower position, just above the cardia, contractile activity was less pronounced and usually less regular than that character-

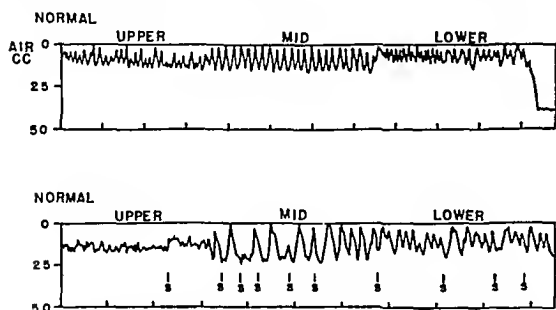


FIG. 1. Records of esophageal motility in two normal subjects. In the lower record the motility pattern is affected by repeated swallowing, indicated by "S."

istic of the mid-position. Details concerning tone and phasic activity are given in Table 1. Figure 1 shows representative records obtained in the three standard positions.

The large waves manifest in the mid- and lower esophagus were decidedly peristaltic in nature. Coincident with their appearance a strong tug was felt at the nasal end of the tube, and fluoroscopic observations showed contraction rings sweeping down over the esophageal balloon. These waves consequently are probably identical with the secondary peristaltic waves described by Meltzer.⁸ The absence of large excursions in records obtained from the upper esophagus is also consistent with Meltzer's observation that secondary waves do not arise in the cervical portion of this organ. Secondary peristaltic waves arising in the mid-esophagus may also be observed by the fluoroscopist when this area is distended by fluid contents that either regurgitate from the lower esophagus or remain after a primary wave has passed.

Swallowing, whether voluntary or involuntary, changed but did not abolish the local motility stimulated by the presence of the balloon. (Fig. 1.) In the upper esophagus a large wave frequently was superimposed on the irregular spontaneous motility. In the mid- and lower esophagus

the changes produced depended to some extent on the phase of the spontaneous motility. Swallowing during the phase of relaxation tended to increase the degree of relaxation and delayed the onset of the next wave but this wave thereupon generally was augmented both in height and duration. Swallowing during the phase of contraction yielded less constant results—the wave in progress was sometimes augmented, sometimes inhibited; occasionally the size of the subsequent wave was increased. These observations, on the whole, are in harmony with the concept that a wave of relaxation precedes a wave of contraction.

Carlson and Luckhardt,³ in studying the motility of the human esophagus with a balloon method, recorded small tonic contractions occurring regularly at less than two-second intervals, larger but irregular tonic contractions and occasional peristaltic waves. Since the balloon used in these studies was quite large (condom, 3 to 4 cm. in length), the dissimilarity between our records and those of Carlson and Luckhardt is surprising. The pressures used by these investigators to inflate their balloon was, however, only 3 to 6 cm. of water, about one-fourth the pressures used by us. The higher pressures routinely employed in our studies may stimulate peristaltic waves of such intensity that smaller contractions are obscured or abolished. Records taken by our method at pressures comparable to those used by Carlson and Luckhardt presented irregular patterns—periods of complete phasic inactivity, occasional tonic or peristaltic contractions and small waves occurring about ten to twenty times a minute. Low pressures in the balloon system apparently provide an inconstant stimulus for esophageal motility, and motility records obtained at such pressures are undistinguished by any regular patterns. Higher intrabalon pressures that stimulate more consistent motility patterns seem to be preferable, consequently, in comparing the motor activities of the normal and abnormal esophagus.

PATIENTS

Records of esophageal motility were obtained in patients with cardiospasm, scleroderma and mechanical obstruction of the esophagus. An analysis of these records is given in Table II.

As might be expected the inflated balloon failed to pass into the stomach of the four patients with cardiospasm. In addition, however, esophageal motility was inadequate to carry the balloon from one part of the esophagus to the other. The tone was

TABLE II
ESOPHAGEAL MOTILITY IN PATIENTS WITH ESOPHAGEAL DISORDERS

Subject	Diagnosis	Tone (cc. of air in balloon)			Height of Wave (cc. of air expelled from balloon)			Frequency (No. of waves per minute)		
		Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower
J. K.	Cardiospasm	26	26-31	30	1-2	2-4	1-2	11	11	15
L. S.	Cardiospasm	..	35	35	..	7-10	3-6	..	10	13
W. W.	Cardiospasm	33	32	26	0	2-6	1-8	0	8	14
H. M.	Cardiospasm	..	21	19	..	13-32	10-32	..	4	10
G. R.	Scleroderma	33	37	28	0*	0*	0*	0*	0*	0*
P. H.	Scleroderma	20	28	26	0*	0*	0*	0*	0*	0*
M. H.	Scleroderma	21	19	27	0*	0*	0*	0*	0*	0*
J. L.	Scleroderma	..	16	26	..	0*	0*	..	0*	0*
O. F.	Carcinoma of stomach invading lower end of esophagus	20	22	26	11	12-18	13-15	6	4½	4½
J. O.	Stricture at esophagojejunal junction	6	13	15	3	18	14	7	4	6

* Very small waves occurring fifteen to twenty-four times per minute appear on the record, but these deflections are produced by respiration.

Cardiospasm. Studies of cardiospasm were made in the following patients:

W. W., a male aged seventy-two, had moderate to severe symptoms for two years. X-ray picture was typical of cardiospasm with 1 to 2+ dilatation and mild tortuosity of the esophagus. Cardia was dilated twice with only partial relief obtained.

J. K., a male aged fifty-seven, complained of vague abdominal symptoms. Cardiospasm was an incidental finding. X-ray showed 2 to 3+ dilatation of the esophagus with early "sigmoid" tortuosity of its lower portion. No treatment was necessary.

L. S., a female aged seventy, had symptoms for three years. There was 2+ dilatation of the esophagus with minimal tortuosity. Cardia was dilated twice with bougies but relief was transient.

H. M., a male aged twenty-three, had symptoms for one year. X-ray showed 1 to 2+ dilatation of the esophagus with no tortuosity. Treatment consisted of dietary methods.

diminished in all four patients. In two patients the wave pattern was strikingly decreased and demonstrated an irregular configuration. (Fig. 2.) The record of esophageal motility in patients L. S. and H. M. revealed strong phasic activity but the regular pattern of the normal esophagus was absent. (Fig. 2.) In spite of the difference apparent in their motility records, patients W. W. and J. K. on one hand, and L. S. and H. M. on the other presented similar clinical and roentgenologic manifestations.

As demonstrated by balloon-kymograph records it appears that esophageal motility in patients with cardiospasm has the following characteristics: (1) decreased tone, (2) phasic activity of variable intensity but irregular in configuration and (3) lack of propulsive capacity even if some phasic activity is present.

Scleroderma. Four patients with scleroderma were studied:

M. H., a female aged forty-five, had generalized severe scleroderma since 1941 with Raynaud's phenomena, skin changes and osteomyelitis of the terminal phalanges. There were minimal digestive symptoms. X-ray of the esophagus revealed slight dilatation with absence of all peristaltic activity.

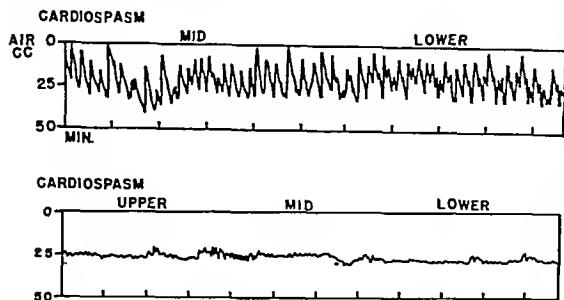


FIG. 2. Records of esophageal motility in two patients with cardiospasm. In the upper record (patient H. M.) phasic activity is strong but irregular. The wave pattern is markedly diminished in the lower record (patient J. K.)

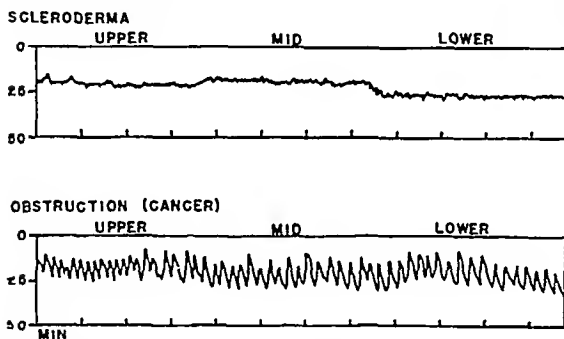


FIG. 3. Records of esophageal motility of patient M. H. with scleroderma (upper record) and of patient O. F. with mechanical obstruction of the esophagus (lower record).

P. H., a female aged fifty-three, had Raynaud's phenomena of the hands for three years. There were minor skin changes of the fingers and hands. Dysphagia, heartburn and diarrhea were pronounced. X-ray revealed moderate dilatation of the esophagus with absence of all peristaltic waves. The small intestine also showed marked hypomotility.

G. R., a male aged fifty-seven, had generalized scleroderma for ten years, with Raynaud's phenomena, skin changes and fibrosis of the lungs. There was occasional diarrhea but no dysphagia. X-ray showed moderate dilatation of the esophagus and absence of all peristaltic waves.

J. L., a female aged forty-three, suffered the onset of Raynaud's phenomena ten years ago. Skin changes which were typical of scleroderma started three and one-half years ago. No dys-



FIG. 4. Roentgenologic appearance of esophagus of patient O. F. The dilatation of the esophagus and the filling defect at its cardiac end can be observed.

phagia or other digestive symptoms were present. X-ray revealed stasis and absence of peristaltic waves in the esophagus but the caliber of the lumen was normal.

In these patients consistent abnormalities of esophageal motility were evident. Propulsion of the inflated balloon down the esophagus was slow or absent, but in one case (P. H.) the balloon slipped from the lower esophagus into the stomach after the patient swallowed. Motility records taken in each of the standard positions showed loss of tone and an absent or markedly diminished wave pattern. (Fig. 3.) It is noteworthy that the esophageal tone of these patients with scleroderma was exceedingly low as measured by the motility records although roentgenologic studies demonstrated only slight or moderate dilatation of the esophagus.

Mechanical Obstruction. Two patients with mechanical obstruction were studied:

O. F., a male aged fifty-three, previously had chronic pyloric obstruction from a duodenal ulcer and developed dysphagia. X-ray showed a moderately dilated esophagus suggest-

ing cardiospasm, but a defect near the cardia indicated neoplasm. (Fig. 4.) Further studies demonstrated carcinoma of the stomach with invasion of the lower esophagus.

J. O., a male aged fifty, developed symptoms of esophageal obstruction following total gastrectomy for cancer of the stomach. X-ray revealed narrowing at the esophagojejunal junction. Mechanical dilatation of that area ameliorated the dysphagia.

In these cases the balloon, after inflation in the upper esophagus, was carried down near the point of obstruction before its progress was arrested. The motility records showed a moderate decrease in tone but the wave pattern was striking in its amplitude and regularity. Although the roentgenologic appearance of the dilated esophagus in patient O. F. was somewhat suggestive of cardiospasm, his motility record showed none of the abnormalities found in this disorder. (Figs. 3 and 4.)

SUMMARY

Balloon-kymograph records of esophageal motility were obtained in subjects with and without clinical disorders of the esophagus. The motility recorded was that stimulated by inflating and maintaining a relatively large balloon in fixed positions of the esophagus.

In subjects without esophageal disorders a characteristic motility pattern was recorded in the upper, middle and lower esophagus, the middle and lower positions

presenting a regular sequence of large peristaltic waves.

In patients with cardiospasm the motility records demonstrated decreased tone and irregular phasic activity of variable intensity. Propulsion of the balloon along the esophagus did not occur.

In patients with scleroderma both tone and phasic activity were markedly diminished. Propulsion of the balloon was diminished but occasionally was present.

Esophageal motility in the presence of mechanical obstruction evidenced a mild decrease in tone and augmented regular phasic activity.

REFERENCES

1. TEMPLETON, F. E. X-ray Examination of the Stomach. Pp. 104. Chicago, 1944. University of Chicago Press.
2. CANNON, W. B. and WASHBURN, A. L. An explanation of hunger. *Am. J. Physiol.*, 29: 441, 1911-1912.
3. CARLSON, A. J. and LUCKHARDT, A. B. Contributions to the physiology of the stomach. X. The condition of the esophagus during the periods of gastric hunger contractions. *Am. J. Physiol.*, 33: 126, 1914.
4. KRONECKER, H. and MELTZER, S. Der Schluckmechanismus, seine Erregung und seine Hemmung. *Arch. f. Anat. u. Physiol.*, supplement, 328, 1893.
5. SCHREIBER, J. Ueber den Schluckmechanismus. *Arch. f. exper. Path. u. Pharmacol.*, 46: 414, 1901.
6. INGELFINGER, F. J. and ABBOTT, W. O. Intubation studies of the human small intestine. xx. The diagnostic significance of motor disturbances. *Am. J. Digest. Dis.*, 7: 468, 1940.
7. HWANG, K., ESSEX, H. E. and MANN, F. C. A study of certain problems resulting from vagotomy in dogs with special reference to emesis. *Am. J. Physiol.*, 149: 429, 1947.
8. MELTZER, S. J. Secondary peristalsis of the esophagus—a demonstration on a dog with a permanent esophageal fistula. *Proc. Soc. Exper. Biol. & Med.* 4: 35, 1906-1907.

II. Cardiospasm, A Generalized Disorder of Esophageal Motility*

PHILIP KRAMER, M.D. and FRANZ J. INGELFINGER, M.D.

Boston, Massachusetts

CURRENT concepts of cardiospasm lean heavily on the psychogenic aspects of this disorder, aspects that were mentioned as early as 1733 when Hoffmann¹ ascribed cardiospasm to "irrational love" and "uncontrolled desires." In spite of the venerability and popularity of the psychogenic theory, however, other hypotheses have had and still have their strong proponents. One group maintains that cardiospasm is the result of mechanical obstruction, whether by fibrosis,² by "liver tunnel,"³ by "diaphragmatic pinchcock"⁴ or by some other lumen-obliterating process. Another group, rather silent of late, favors the view that a primary esophageal atony is responsible.⁵ Perhaps most popular is Meltzer's⁶ idea,† seconded or re-conceived by Einhorn,⁷ Rolleston,⁸ Hurst⁹ and Alvarez,¹⁰ that a neuromuscular dysfunction prevents receptive relaxation of the cardia before an advancing peristaltic wave. The cause for such dysfunction has been found in congenital abnormalities,¹³ nutritional deficiencies^{14,15} and emotional states.¹⁶⁻¹⁸

One reason for this plethora of contradictory hypotheses is the failure to define

†Hurst and Rake¹¹ stated that Meltzer, like von Miculiz,¹² ascribed cardiospasm to a "spasmodic contraction of the cardiac sphincter." Actually Meltzer⁶ wrote as follows, ". . . the cardia is under ordinary circumstances moderately contracted. At the beginning of swallowing, the cardia relaxes, . . . If the relaxing force were for any reason weakened or completely inhibited, the cardia would be considerably contracted in the non-swallowing phase (and would) not relax during the act of swallowing . . ." Thus he postulated a contraction of the cardia in his case because "the relaxing inhibitory force was suddenly weakened or completely abolished." These statements certainly embody the concept of Hurst's achalasia.

the clinical condition usually known as cardiospasm. In some studies, for example, any esophageal spasms or any delays in the passage of material down the esophagus are considered as the equivalents of clinical cardiospasm. This practice ignores the findings of such experienced observers as Plummer and Vinson¹⁹ who separated their patients with "cardiospasm" into two groups: (1) those suffering from chronic if not continuous symptoms and manifesting some esophageal dilatation and (2) those with transient, irregular spasms, not necessarily located at the lower esophagus and not accompanied by luminal enlargement. A further separation of these two groups has been made by Templeton²⁰ who pointed out that cardiospasm is not only a disorder of the lower end of the esophagus but that the motility of the whole esophagus, as judged fluoroscopically and roentgenologically, is markedly deranged. As a matter of fact, Templeton has never seen a case of cardiospasm with normal esophageal motility.²¹ Our studies, which support, and amplify Templeton's views, indicate that the clinical condition of cardiospasm can be defined more precisely and that it should not be confused with transient spasm, mechanical obstruction or other esophageal disorders.

Studies were carried out in four patients with cardiospasm, in four with scleroderma and in two with mechanical obstruction of the esophagus. Brief abstracts of these cases are given in our previous paper.²² In addition the following two patients were studied:

* From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

J. P. was a female aged thirty-one. A diagnosis of cardiospasm was made in 1945 following the onset of dysphagia in 1944. Periodic dilatation with bougies was done; there was relief of the symptoms for several months after each treatment. Raynaud's phenomena of the hands

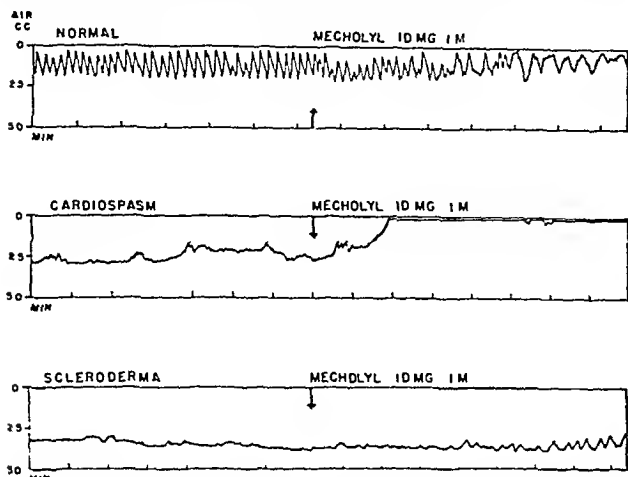


FIG. 1. Effect of 10 mg. of acetylbetamethylcholine chloride on esophageal motility. Upper record, control subject; middle record, patient J. K. with cardiospasm; lower record, patient G. R. with scleroderma.

began in 1945, accompanied by skin changes on the chest and back suggestive of scleroderma. X-ray of the esophagus at our hospital showed minimal dilatation, absence of all peristaltic waves and slight stasis.

R. F. was a male aged twenty-four. For two years the patient had transient and brief attacks of the sensation of food sticking in the lower esophagus; the sensation came on during periods of emotional tension. X-ray examination during an attack showed spasm of the esophagus 1 inch above the diaphragm. Peristaltic activity was normal and no dilatation was present. There were normal esophageal outlines and motility between the attacks.

In each of these cases the motility of the esophagus was studied by balloon-kymograph methods as well as by fluoroscopic and roentgenologic means.

As described previously,²² esophageal motility in cases of cardiospasm displays (1) decreased tone, (2) lack of propulsion and (3) an abnormal wave pattern. The phasic activity may be forceful or weak, but its configuration is irregular and even strong phasic activity is inadequate to propel the esophageal balloon. These changes occur in both the mid- and lower esophagus, areas where the normal esophagus exhibits strong

and effective propulsive waves. The motility pattern of cardiospasm is different from that found in other clinical disorders of esophageal motor function. In scleroderma the tone is depressed, as in cardiospasm, but phasic activity is practically absent. In

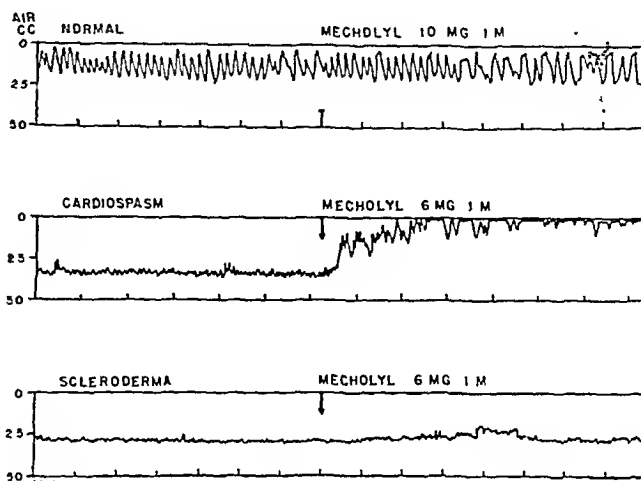
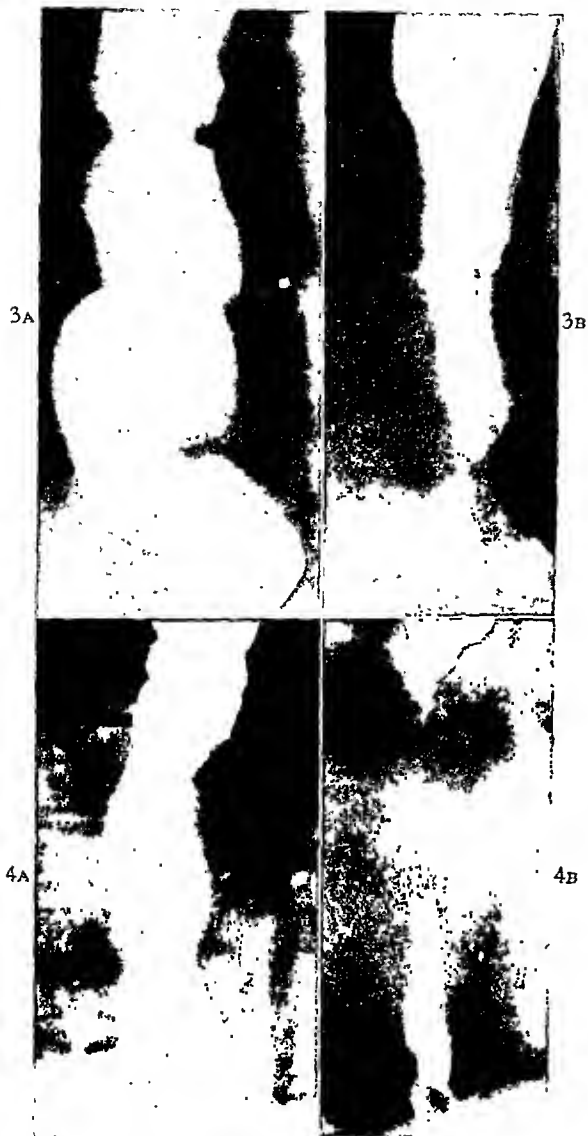


FIG. 2. Effect of acetylbetamethylcholine chloride on esophageal motility; 10 mg. given to control subject (upper record) and 6 mg. each to patient L. S. with cardiospasm (middle record) and patient P. H. with scleroderma (lower record).

mechanical obstruction of the distal esophagus large peristaltic waves of normal shape and arrangement may occur even if secondary dilatation proximal to the point of obstruction has taken place. The record of esophageal motility in patient R. F., with transient spasms of the lower esophagus, was normal in all respects and did not resemble that seen in patients with cardiospasm.

After suitable control records were obtained acetylbetamethylcholine chloride was given intramuscularly in 6 to 10 mg. doses to four control subjects, four patients with cardiospasm, two patients with scleroderma and patient J. P. The effect of this drug in patients with cardiospasm was startling for within two minutes of its administration a tonic, lumen-obliterating contraction of the esophagus took place. This contraction was of sufficient intensity to counteract a pressure of 20 cm. of water and to force all of the air out of the recording balloon. (Figs. 1 and 2.) The same effect could also be observed roentgenologically; after administration of acetylbetamethylcholine chloride even a considerably dilated esoph-



FIGS. 3A and B. Effect of acetylbetamethylcholine chloride on roentgenologic appearance of esophagus in patient J. K. with cardiospasm. A, before; B, three minutes after administration of 10 mg. of acetylbetamethylcholine chloride.

FIGS. 4A and B. Effect of acetylbetamethylcholine chloride on roentgenologic appearance of esophagus in patient W. W. with cardiospasm. A, before; B, three minutes after administration of 10 mg. of acetylbetamethylcholine chloride.

agus contracted to form a narrow lumen containing a thin thread of barium. (Figs. 3 and 4.) The tonic contraction, however, forced little material through the cardia. Instead, the esophageal content, whether a barium suspension or a recording balloon, was displaced backward into the upper esophagus. At the time of the tonic contraction the patient frequently experienced

substernal distress similar to the pain occasionally produced by the ingestion of food.

In normal subjects acetylbetamethylcholine produced some increase in tone but the effect was far less marked than that seen in patients with cardiospasm. (Figs. 1 and 2.) In patients with scleroderma the esophagus responded very little to injections of acetylbetamethylcholine; only minimal increases in phasic activity and tone were observed. (Figs. 1 and 2.) Patient J. P., who had been treated as a case of cardiospasm but who subsequently developed Raynaud's phenomena and skin changes suggesting scleroderma, responded to mecholyl as did the patients with clearcut scleroderma; that is, the esophageal motility evidenced very little alteration following injection of the drug.

COMMENTS

The number of patients studied is not large but tentative suggestions concerning the diagnosis and nature of cardiospasm seem permissible. The character of the esophageal motility record and the response to acetylbetamethylcholine appear to be sufficiently specific to differentiate at least a certain group of patients with cardiospasm from normal subjects and from patients afflicted with scleroderma, mechanical obstruction or transient spasms of the esophagus. This differentiation is not always simple by clinical and roentgenologic means. Cancer of the gastric cardia, for example, may produce a roentgenologic appearance of the esophagus that mimics cardiospasm closely. Our patient O. F., a case in point, exhibited a normal if hyperactive motility record, and it will be interesting to ascertain whether the motility records of all such patients are normal in contradistinction to the records of patients with cardiospasm. Finally, the response to acetylbetamethylcholine may provide a means of differentiating esophageal stasis produced by cardiospasm from that caused by scleroderma. Patient J. P. provides an example of a patient treated for cardiospasm, but the development of Raynaud's phenomena and

skin changes, as well as the negative esophageal response to parasympathetic stimulation, suggests that the correct diagnosis may have been scleroderma.

The motor abnormalities found in our patients with cardiospasm clearly involve both the mid- and lower esophagus, thereby indicating that the esophageal disorder in this condition is not merely confined to the cardiac end but that a motor dysfunction involves nearly the entire esophagus. The finding of abnormal wave patterns, which may be intense but so disorganized that propulsion is inadequate, can be accepted as strong evidence against the theories that cardiospasm is caused either by a primary neuromuscular atony of the esophagus or by some mechanical obstruction which produces secondary dilatation of the lumen. Furthermore, in our two patients with mechanical obstruction near the cardia, secondary dilatation was not accompanied by irregular phasic activity; on the contrary, the normal wave pattern was accentuated and augmented. No direct evidence either for or against the theory of achalasia is adduced by these studies. It would seem reasonable to postulate, however, that achalasia of the cardia is a feature of cardiospasm but that it represents only one abnormality in a neuromuscular dysfunction which involves nearly the entire esophagus.

The hypersensitive response to mecholyl evidenced by the esophagus in patients with cardiospasm can be advanced as another argument favoring the presence of a neuromuscular dysfunction in this condition. According to Cannon's law, destruction of a unit in a series of efferent neurons is followed by an increased irritability to chemical agents in the isolated structure or structures, the effect being maximal in the part directly denervated.²³ Viewed in light of this law the hypersensitivity of the cardiospastic esophagus to a parasympathomimetic agent suggests that the parasympathetic innervation of the esophagus has been disrupted somewhere along its course. Such a suggestion is in keeping with

the findings of those neuropathologists who maintain that a degeneration and decrease in the number of the intramural ganglia occur in cardiospasm.²⁴⁻²⁶ Whether a disorder of the parasympathetic nervous system is the primary or the only disorder responsible for cardiospasm remains to be seen. It is of interest, however, that spasms of the lower esophagus have been repeatedly described as one of the complications of vagal section carried out for the treatment of peptic ulcer.²⁷⁻³³ In our case, as well as in the other cases reported, the symptoms and findings subsided spontaneously within a few weeks. Unfortunately, motility records were not obtained in our patient with spasm of the lower esophagus following vagal section.

Although these studies indicate that cardiospasm is characterized by a generalized dysfunction of esophageal motility and that it may be produced by a disruption of the parasympathetic innervation, the ultimate cause of this condition remains obscure. That psychogenic stimuli may be responsible is consistent with the observations that have been made. On the other hand, since cardiospasm appears to be such a generalized esophageal disorder, it is questionable whether the production of isolated spasms in the esophagus, or of delays in swallowing time by the use of emotional stimuli can be used as arguments in favor of the psychogenesis of cardiospasm.^{34,35} The two conditions, namely, the clinical state of cardiospasm and isolated spasms of the esophagus appear unrelated to us. It may, of course, be argued that a gradual transition occurs from isolated spasms of the esophagus to well established cardiospasm³⁶ but such a transition is not generally described by experienced observers and, according to Vinson,^{29,37} probably does not occur. Further observations, however, will be necessary to settle this point.

Since the esophagus in cardiospasm appears to be hypersensitive to acetyl-beta-methylcholine, it is likely that it may also be hypersensitive to humoral agents

elaborated under conditions of emotional stress. The demonstration, therefore, that the symptoms of cardiospasm are accentuated by psychogenic stimuli can be accepted as evidence of the irritability and hypersensitivity of the esophagus in this condition, but it has relatively little validity as evidence purporting to show that cardiospasm is a psychogenic disorder. In this connection it must also be remembered that cardiospasm may be present as an asymptomatic condition as it was, for example, in our patient J. K. Hence, the frequent observation that the initial symptoms of cardiospasm may arise at the time of some emotional trauma is again of questionable etiologic significance. Such patients may well suffer from latent cardiospasm which is accentuated at the time of mental stress.

SUMMARY

In four patients with cardiospasm the esophageal motility as studied by balloon-kymograph records presented the following deviations from normal: decreased tone, lack of propulsion and irregular phasic activity of variable intensity. These abnormalities involved the lower two-thirds of the esophagus.

Administration of acetylbetamethylcholine chloride to patients with cardiospasm produced a violent tonic contraction of the lower half of the esophagus. This contraction obliterated even a considerably dilated lumen.

The esophageal motility pattern and the hypersensitive response to acetylbetamethylcholine chloride differentiated the esophageal motility of cardiospasm from that recorded in control subjects and in patients with scleroderma, mechanical obstruction of the esophagus and transient spasms of the esophagus.

The diffuse derangement of esophageal motility found in the patients with cardiospasm suggests that this disorder affects not only the cardia but nearly the entire esophagus. The hypersensitive response to a parasympathicomimetic agent, when viewed in light of Cannon's law of denervation,

supports the hypothesis that disruption of the esophageal parasympathetic innervation plays a role in the pathogenesis of cardiospasm.

The observations made do not elucidate the ultimate cause of cardiospasm. They indicate, however, that cardiospasm should be more precisely defined and should not be confused with other disorders of esophageal motility. They furthermore indicate that some of the arguments which have been advanced in favor of the view that cardiospasm is a psychogenic disorder must be accepted with some reservation.

REFERENCES

1. HOFFMANN, F.¹⁶
2. MOSHER, H. P. The esophagus. *Surg., Gynec. & Obst.*, 60: 403, 1935.
3. MOSHER, H. P. The liver tunnel and cardio-spasm. *Laryngoscope*, 32: 348, 1922.
4. JACKSON, C. The diaphragmatic pinchcock in so-called "cardiospasm." *Laryngoscope*, 32: 139, 1922.
5. ROSENHEIM, T. Beiträge zur Oesophagoskopie. II. Ueber einige seltenere Oesophagealerkrankungen und ihre diagnostische Abgrenzung vom Krebs. *Deutsche med. Wchnschr.*, 25: 53, 75, 1899.
6. MELTZER, S. G. Ein Fall von Dysphagia nebst Bemerkungen. *Berlin klin. Wchnschr.*, 25: 140, 173, 1888.
7. EINHORN, M. A case of dysphagia with dilatation of the esophagus. *M. Rec.*, 34: 751, 1888.
8. ROLLESTON, H. P. Simple dilatation of the oesophagus. *Tr. Path. Soc. London*, 47: 37, 1896.
9. HURST, A. F. Achalasia of the cardia. *Quart. J. Med.*, 8: 300, 1915.
10. ALVAREZ, W. C. An Introduction to Gastro-enterology. Pp. 197, 283. New York, 1940. P. B. Hoeber, Inc.
11. HURST, A. F. and RAKE, G. W. Achalasia of the cardia (so-called cardiospasm). *Quart. J. Med.*, 23: 491, 1930.
12. VON MICULICZ, J. Zur Pathologie und Therapie des Cardiospasmus. *Deutsche med. Wchnschr.*, 30: 17, 50, 1904.
13. FLEINER, W. Neue Beiträge zur Pathologie der Speiseröhre. *München. med. Wchnschr.*, 47: 529, 578, 1900.
14. ETZEL, E. May disease complex that includes megacolon (cardiospasm), megacolon and megacystitis be caused by chronic vitamin B₁ deficiency? *Am. J. M. Sc.*, 203: 87, 1942.
15. MERRILL, D. and RICHARDS, R. Dysphagia and nutritional deficiency. *New England J. Med.*, 225: 326, 1941.
16. THIEDING, F. Ueber Cardiospasmus, Atonic und "idiopathische" Dilatation der Speiseröhre. *Beitr. z. klin. Chir.*, 121: 237, 1921.
17. WEISS, E. Cardiospasm: a psychosomatic disorder. *Psychosom. Med.*, 6: 58, 1944.
18. MOSCHCOWITZ, E. Essays on the biology of disease. *J. Mt. Sinai Hosp.*, 13: 337, 1947.

19. PLUMMER, H. S. and VINSON, P. P. Cardiospasm: a report of 301 cases. *M. Clin. North America*, 5: 355, 1921.
20. TEMPLETON, FREDERIC E. Movements of the esophagus in the presence of cardiospasm and other esophageal discases. A roentgenologic study of muscular action. *Gastroenterology*, 10: 96, 1948.
21. TEMPLETON, F. E. Personal communication.
22. KRAMER, P. and INGELFINGER, F. J. Motility of the human esophagus in control subjects and in patients with esophageal disorders. *Am. J. Med.*, 7: 168, 1949.
23. CANNON, W. B. A law of denervation. *Am. J. M. Sc.*, 198: 737, 1939.
24. RAKE, G. W. On the pathology of achalasia of the cardia. *Guy's Hosp. Rep.*, 77: 141, 1927.
25. LENDRUM, F. D. Anatomic features of cardiac orifice of the stomach with special reference to cardiospasm. *Arch. Int. Med.*, 59: 474, 1937.
26. ETZEL, E. Megaoesophagus and its neuropathology. A clinical and anatomo-pathological research. *Guy's Hosp. Rep.*, 87: 158, 1937.
27. CARLSON, A. J. Discussion of GRIMSON, K. S., TAYLOR, H. M., TRENT, J. C., WILSON, D. A. and HILL, H. C. The effect of transthoracic vagotomy upon the functions of the stomach and upon the early clinical course of patients with peptic ulcer. *South. M. J.*, 39: 460, 1946.
28. INGELFINGER, F. J. Discussion of TEMPLETON, F. E. The esophagus—some roentgenologic observations of the muscular action in the normal and abnormal. *Proc. New England Roentgen Ray Soc.*, 3: 1, 1946.
29. VINSON, P. P. Diagnosis and treatment of cardiospasm. *South. M. J.*, 40: 387, 1947.
30. GRIMSON, K. S., BAYLIN, G. J., TAYLOR, H. M., HESSER, F. H. and RUNDLES, R. W. Transthoracic vagotomy. The effects in 57 patients with peptic ulcer and the clinical limitations. *J. A. M. A.*, 134: 925, 1947.
31. MOSES, W. R. Critique on vagotomy. *New England J. Med.*, 237: 603, 1947.
32. RITVO, M. and SHAUFFER, I. A. Roentgenographic studies of the gastrointestinal tract following section of the vagus nerves for peptic ulcer. *New England J. Med.*, 238: 496, 1948.
33. MEYER, K. A., ROSI, P. A. and STEIN, I. F., JR. Studies on vagotomy in the treatment of peptic ulcer. II. Clinical evaluation. *Surg., Gynec. & Obst.*, 86: 524, 1948.
34. FAULKNER, W. B., JR. Objective esophageal changes due to psychic factors. An esophagoscopy study with report of 13 cases. *Am. J. M. Sc.*, 200: 796, 1940.
35. WOLF, S. and ALMY, T. P. Experimental production of cardiospasm in human subjects. The American Gastroenterologic Association, May 1, 1948.
36. VERBRYCKE, J. R., JR. Cardiospasm, with report of 100 cases. *South. M. J.*, 13: 236, 1920.
37. VINSON, P. P. Personal communication.

Treatment of Chronic Non-specific Ulcerative Colitis with Aureomycin*

A Preliminary Report

JEROME A. MARKS, M.D., LOUIS T. WRIGHT, M.D. AND SELIG STRAX, M.D.

New York, New York

ALTHOUGH the primary etiologic agent in most cases of ulcerative colitis is unknown, the secondary infection which develops when the mucosal barrier is broken^{1,2} greatly contributes to the clinical picture and the serious pathologic changes of this disease. No specific pathogen has been implicated despite attempts to prove an etiologic relationship with *Bacillus dysenteriae*^{3,4} or with *Diplostreptococcus* of Bargen.^{5,6} Rather, a wide variety of organisms has been cultured from the stool, including hemolytic and non-hemolytic *Escherichia coli*, hemolytic and non-hemolytic streptococci, enterococci and *Staphylococcus aureus*.¹ In an attempt to combat this non-specific secondary infection which plays so important a part in ulcerative colitis, chemotherapy and antibiotics in various forms have been much employed. For this reason it seemed expedient to note the effects of a new and potent antibiotic, aureomycin.

Aureomycin, which was discovered by Duggar⁷ and his associates, is derived from the mold *Streptomyces aureofaciens* and possesses bacteriostatic and bactericidal activity for a number of gram-positive and gram-negative organisms, including some penicillin- and streptomycin-resistant organisms.⁸ It also possesses virucidal properties⁹ and we have reported favorably on its use in the treatment of lymphogranuloma venereum. Its toxicity is low, the lethal dose in mice being between 3,000 and 4,000 mg. per Kg. of body weight.¹⁰ In solution the hydrochloride salt is acid and intramuscular

injections may be irritating. It may be given intravenously in doses from 200 mg. to 1 Gm. in 500 cc. of 5 per cent glucose in distilled water. Oral administration of 250 or 500 mg. three or four times a day produces effective blood levels for twelve to thirty hours. Occasional nausea is encountered and may be alleviated or prevented with aluminum hydroxide.

We had obtained what seemed to be good results with aureomycin in a case of pyoderma gangrenosum occurring in a patient with chronic non-specific ulcerative colitis, the case having been previously reported.¹¹ The effects on the condition of the colon in this case were sufficiently impressive to warrant further study of the clinical effects of aureomycin in chronic non-specific ulcerative colitis.

PATIENTS, MATERIALS AND METHODS

The patients represented an unselected series and most of them had been under observation by one of us (J. A. M.) for long periods of time. All had been carefully studied by the usual methods of x-ray, sigmoidoscopy, stool culture and examination for parasites so that the diagnosis of idiopathic ulcerative colitis had been established to the exclusion of any other.

Aureomycin (as a hydrochloride) was given orally in 250 mg. capsules, one every eight hours. If after one or more weeks there was no change in the clinical course, the dose was doubled; or *per contra*, if in several weeks there was significant improvement, the dose was reduced to one capsule once or twice daily. No other drugs were used except occasional small doses of belladonna and phenobarbital. A low-residue bland diet was prescribed.

* From The Surgical and Medical Services, Harlem Hospital, Department of Hospitals, New York, N. Y.

Observations were directed solely toward the clinical response to the drug. These included, particularly, variation in the number of stools after treatment commenced, presence of blood in the stools, gain or loss in weight by the patient, variation in the sigmoidoscopic ap-

CASE 1. H. M., was a male aged thirty-nine. The onset of diarrhea was in June, 1947, with ten to twelve movements daily. From then until the summer of 1948 he had seven to eight bowel movements a day and in October, 1948, they increased to fifteen and occasionally to twenty-

TABLE I
SUMMARY OF ACTIVE CASES OF ULCERATIVE COLITIS

No.	Name	Age	Sex	Duration of Disease	Duration of Treatment	Stools						After Treatment		
						No.		Blood		Character				
						Before Aureomycin	After Aureomycin	Before Aureomycin	After Aureomycin	Before Aureomycin	After Aureomycin	Weight Gained (pounds)	Well Being	Sigmoidoscopy Improved
1	H. M.	39	M	18 mo.	12 weeks	25	2	+	0	Watery	Formed	24	++++	+
2	E. K.	23	F	5 yr.	13 weeks	8	2	+	0	Watery	Formed	20	++++	+
3	J. C.	20	M	14 yr.	13 weeks	13	6	+	0	Watery	Formed	28	++++	+
4	L. M.	21	M	6 yr.	7 weeks	6	3	+	±	Soft	Formed	17	++	0
5	H. M.	19	M	12 mo.	11 weeks	7	2	+	0	Soft	Formed	25	++++	+
6	B. C.	42	M	18 yrs.	6 weeks	8	4	+	0	Soft	Formed	9	++++	+
7	E. G.	50	M	2 yr.	5 weeks	7	2	+	0	Soft	Formed	0	+++	0
8	J. A.	33	F	5 yr.	4 weeks	9	4	+	0	Watery	Formed	0	++	0
9	S. H.	42	M	1 mo.	12 weeks	3	2	+	0	Watery	Formed	4	++	+
10	R. R.	44	F	4 yr.	3 weeks	10	2	+	0	Watery	Semi-formed	-1	+	0
11	L. R.	45	M	5 yr.	11 weeks	6	2	+	0	Semisoft	Formed	0	+++	+
12	A. G.	32	M	12 yr.	9 weeks	9	5	+	±	Soft	Semi-formed	0	++	Not done
13	C. C.	28	F	1 yr.	5 weeks	8	3	+	0	Soft	Soft	-12	+	0

TABLE II
SUMMARY OF QUIESCENT CASES OF ULCERATIVE COLITIS

No.	Name	Age	Sex	Duration of Disease	Duration of Treatment	Stools						After Treatment		
						No.		Blood		Character				
						Before Aureomycin	After Aureomycin	Before Aureomycin	After Aureomycin	Before Aureomycin	After Aureomycin	Weight Gained (pounds)	Well Being	Sigmoidoscopy Improved
14	J. C.	38	M	18 yr.	9 weeks	3	3	+	±	Soft	Semi-formed	5	+	0
15	H. C.	28	M	11 yr.	7 weeks	2	2	+	±	Soft	Formed	8	+	+

pearance and, finally, subjective observations on the patient's sense of "well being." No studies were made on changes in the bacterial flora or in the roentgen appearance of the colon. These will appear at a later time.

CASE REPORTS

The significant clinical features of each case are briefly presented in the following histories and summarized in Tables I and II. In addition, several of the cases are presented graphically in Figures 1 to 9.

AUGUST, 1949

five or thirty daily. This was accompanied by a 25-pound weight loss. The past history includes an operation for perforated peptic ulcer in 1930, an undiagnosed hemorrhage from the rectum in 1939, an appendectomy in 1946, a subtotal gastrectomy in November, 1946, with recurrence of ulcer symptoms early in 1947, for which vagotomy and splenectomy were performed.

He was admitted to Harlem Hospital on November 18, 1948, at which time he was having as many as twenty-five bowel movements

daily. Aureomycin, 250 mg. every eight hours, was given and on his discharge three weeks later the movements averaged two daily. Following discharge aureomycin was discontinued and the movements increased to three or four a day. When aureomycin was resumed, the stools be-

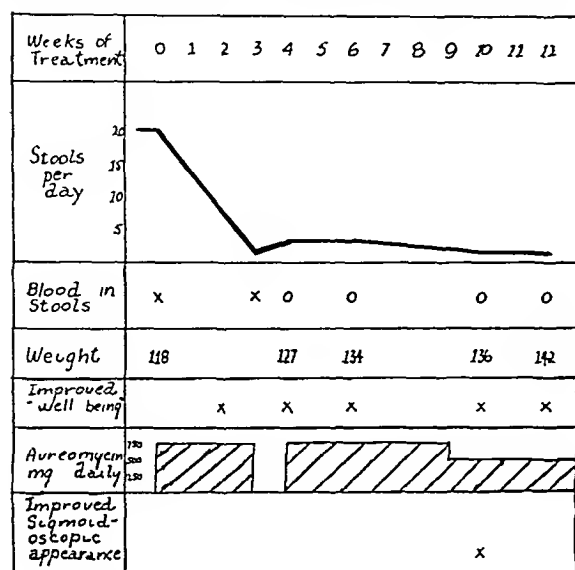


FIG. 1. Case I. H. M., male, thirty-nine years old.

came formed again and were reduced to two daily, with a dose of 750 mg. daily. The movements continued to be formed and remained at two daily when aureomycin was reduced to 250 mg. twice a day in the tenth week of treatment.

Sigmoidoscopy prior to his hospitalization showed a swollen congested mucosa. When sigmoidoscopy was repeated on January 21, 1949, the rectum and lower sigmoid colon showed no abnormalities. His weight increased from 118 to 142 pounds.

CASE II. E. K., was a female aged twenty-three. The onset of diarrhea in 1943 was associated with some bleeding, averaging six to eight movements daily. This continued on and off to date and was usually aggravated by an emotional disturbance. Barium colon enema in May, 1944, indicated chronic ulcerative colitis involving the entire colon and repeated sigmoidoscopies showed findings typical of this condition. In March, 1948, she had a complete check-up at Mercy Hospital, Rockville Center, where the diagnosis of colitis was again established. Proctoscopic examination in October, 1948, showed typical granular ulcerating, congested, bleeding mucosa.

The patient was admitted to Harlem Hospital on November 10, 1948, at which time she was

averaging seven to eight bowel movements a day. Aureomycin, 250 mg. every eight hours, was given and continued until discharge from the hospital on December 1, 1948, when she was having two formed bowel movements daily without blood. Sigmoidoscopy revealed an almost normal colon. After being without aureomycin for two weeks her bowel movements increased to four a day but were promptly reduced to one or two daily upon resumption of the drug. Proctoscopy on January 13, 1949, revealed an entirely normal mucosa. Aureomycin was discontinued and the movements increased to four soft stools daily but returned to two formed movements when 250 mg. of aureomycin were given daily for one week. Aureomycin has been discontinued and the stools remain formed and occur twice daily.

CASE III. J. C., a male aged twenty, has had diarrhea since 1934 when, at the age of five, he first had ten to twelve bowel movements a day containing pus, blood and mucus. He was fairly well until about 1941 when he again began to have diarrhea and had numerous recurrences until 1942 when he developed a fistula in ano. From 1943 to early 1947 he averaged about six movements a day. In the spring of 1947 his bowel movements increased to eight or nine daily. This increase continued so that when first seen on August 8, 1948, he was having thirteen bowel movements a day. A barium colon enema done in 1943 showed ulcerative colitis and x-ray studies in August, 1948 confirmed this diagnosis. Repeated sigmoidoscopies showed severe chronic ulcerative colitis.

Aureomycin, 250 mg. every eight hours, was commenced on December 4, 1948, and in one week caused a decrease in the number of bowel movements from thirteen to seven daily. On January 21, 1949, aureomycin was increased to 1,500 mg. daily, and in the following week stools averaged six per day. He was kept on this regimen until February 19th, during which time there was no significant change when aureomycin was reduced to 750 mg. a day. On this dosage he averaged about four movements daily, all without blood, "feels better than ever before" and has gained 28 pounds since initiation of aureomycin therapy. He was particularly gratified by his improvement since it took place while he was carrying a heavy program at college which was not interrupted during final examinations, at which time in the past he always had had an exacerbation of the disease.

CASE IV. L. M., a male aged twenty-one, was first seen in 1942 at the age of fourteen when he was having twelve bloody movements daily associated with fever and chills. In the last six years he averaged six soft, frequently bloody

movements daily, despite a severe cold which (as just noted) usually aggravated his diarrhea. He had no pain and there was less blood in the stool. He had gained 17 pounds in weight in seven weeks.

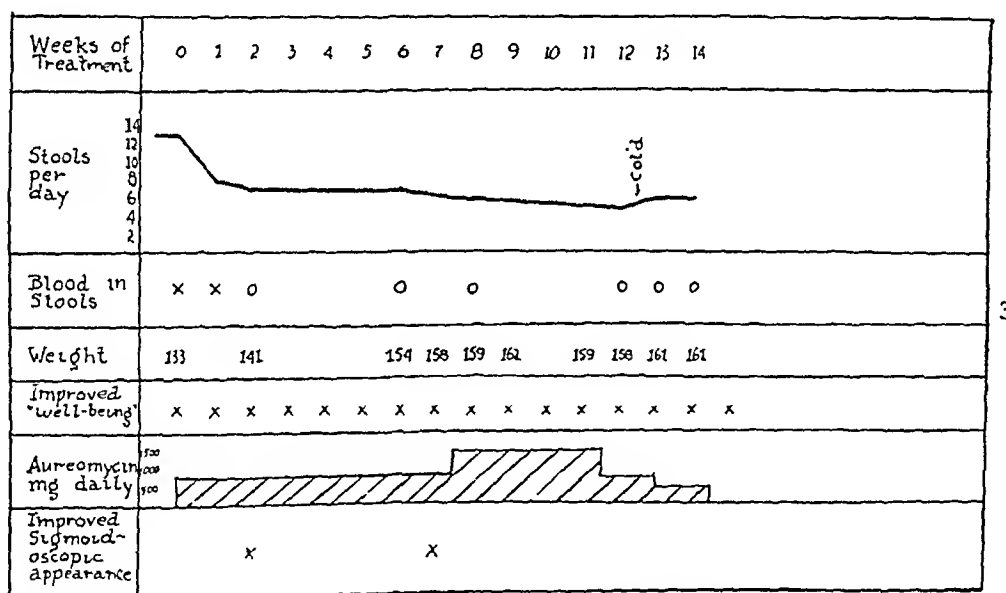
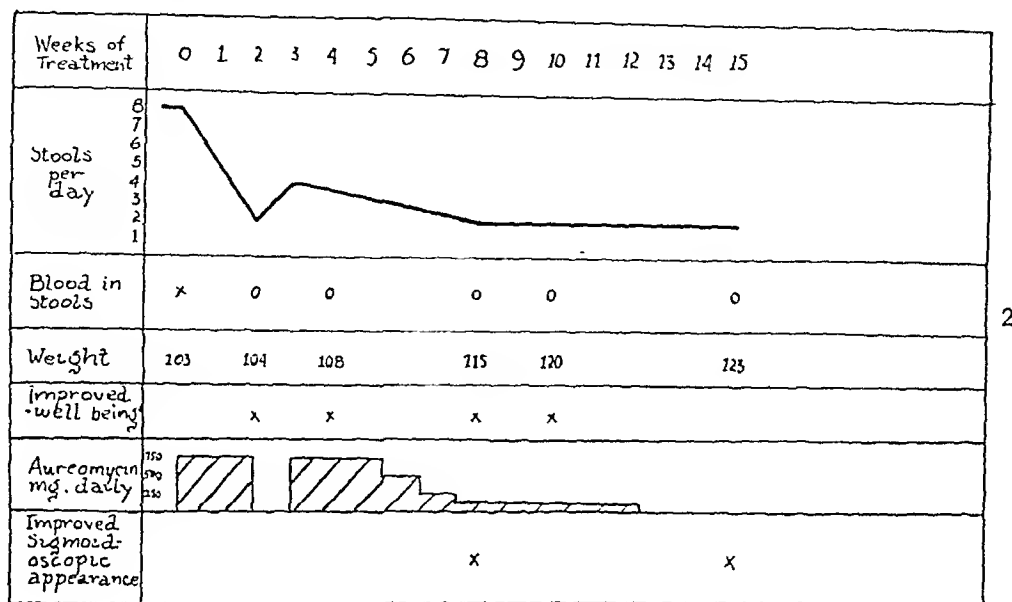


FIG. 2. Case II. E. K., female, twenty-three years old.

FIG. 3. Case III. J. C., male, twenty years old.

movements a day. Recently there has been considerable weight loss and blood in every movement. Whenever he had a common cold, movements increased to twenty daily. Sigmoidoscopy on January 15, 1949, revealed diffuse congestion, many small bleeding points and, at 1 and 5 inches from the anus, small, flat polypoid growths. At this time he was given aureomycin, 250 mg. every eight hours.

During the first three weeks there was little change either in bowel movements or subjective sensation but in the fourth week he showed definite improvement, with two to three soft

CASE V. H. M. was a male aged nineteen. The onset of bloody stools was in October, 1947. In December, 1947, barium enema revealed chronic ulcerative colitis. About this time his bowel movements increased to eight daily, and he was admitted in January, 1948, to the Israel Zion Hospital (Brooklyn), where the diagnosis was confirmed, for intravenous feedings. Aureomycin therapy was initiated on December 11, 1948, at which time he was having seven mushy, bloody movements daily. Sigmoidoscopy showed a granular, congested, easily bleeding mucosa.

The following week his movements were

formed and reduced to three daily without blood. Aureomycin has been continued and he now averages two movements a day without blood. Sigmoidoscopic examination on January 22, 1949, revealed no congestion or edema but there was an occasional bleeding point. On

revealed a normal mucosa up to 7 inches. His weight increased from 127 to 153 pounds. He is now carrying a full college program and states that he feels "wonderful."

CASE VI. B. C. was a male aged forty-two. For the past eighteen years the patient has had

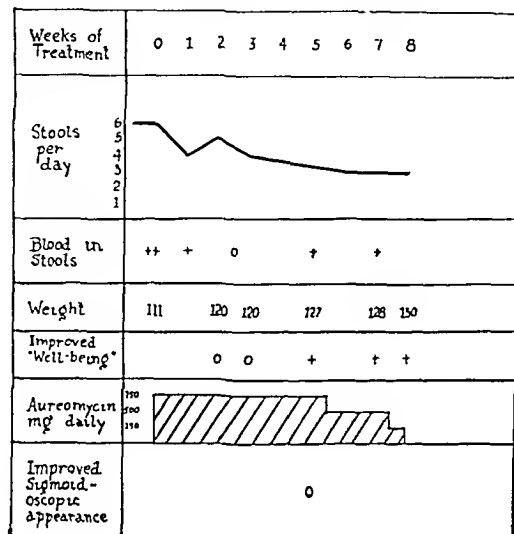


FIG. 4

FIG. 4. Case iv. L. M., male, twenty-one years old.

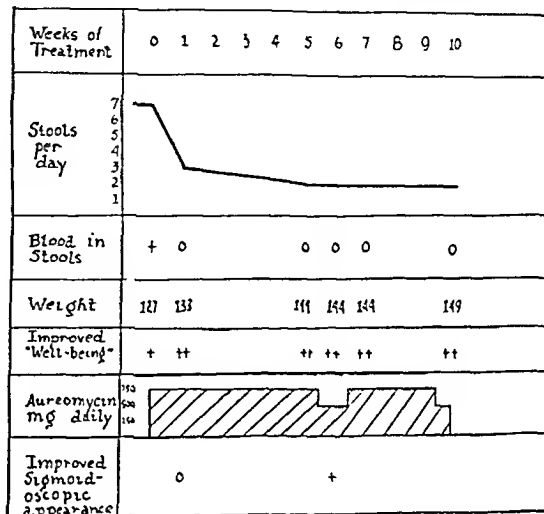


FIG. 5

FIG. 5. Case v. H. M., male, nineteen years old.

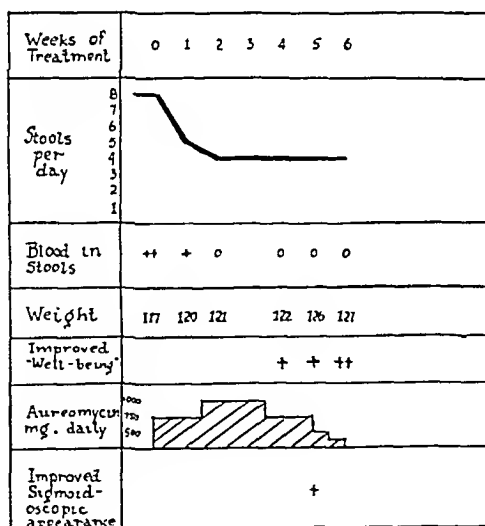


FIG. 6

FIG. 6. Case vi. B. C., male, forty-two years old.

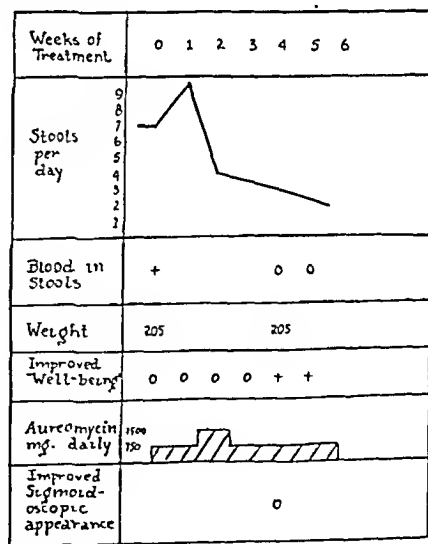


FIG. 7

FIG. 7. Case vii. E. G., male, fifty years old.

February 19, 1949, aureomycin was reduced to 500 mg. daily and one week later to 250 mg. daily. The movements continued to be well formed, without blood and average two daily. He was free from any pain or tenesmus which had previously been a most troublesome symptom. Sigmoidoscopy on February 27, 1949,

annual bouts of bloody diarrhea lasting three months. Repeated sigmoidoscopies and barium enemas revealed typical findings of ulcerative colitis. During the last seven years he was having about eight soft, bloody movements daily but stated that his true bowel habit would be about twelve to fourteen stools a day were it not for the

Tr. Opii which he had been taking steadily. This was discontinued and aureomycin, 250 mg. every eight hours, was given beginning January 22, 1949. On January 29, 1949, the bowel movements were five a day, slightly more formed and with less blood. Aureomycin was increased to

tremely congested, edematous bleeding mucosa with a thick purulent discharge. Aureomycin, 250 mg. every eight hours, was started. Four days later he again had a cold and the stools increased to ten daily. Aureomycin was increased to 1,500 mg. daily. In the next three to

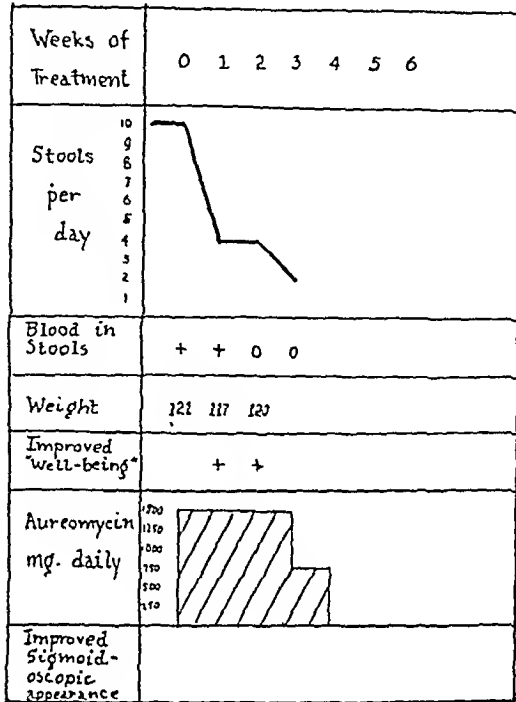


FIG. 8

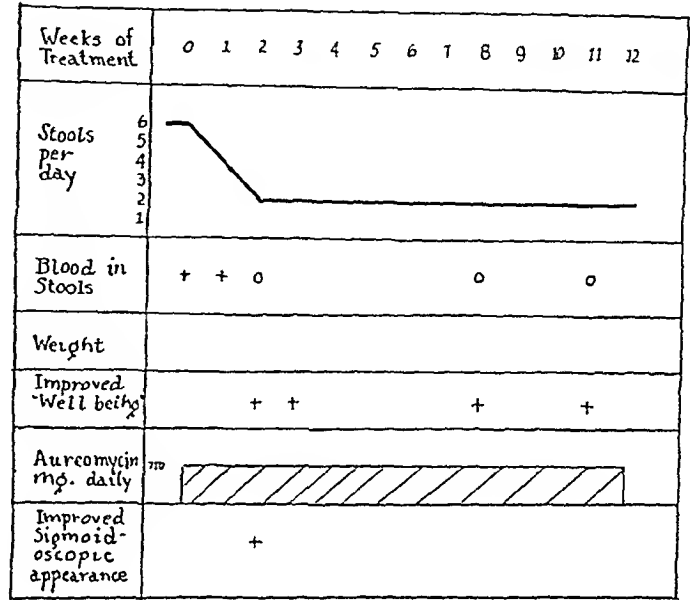


FIG. 9

FIG. 8. Case x. R. R., female, forty-four years old.

FIG. 9. Case xi. L. R., male, forty-five years old.

1,000 mg. a day. During the next three weeks he felt better and was having three to five semi-formed movements daily, free of blood. Aureomycin was reduced to 750 mg. daily. The stools continued at four daily, were fairly well formed and free of blood. Subjectively he felt much stronger, was free of tenesmus, had had no "accidents" and was 9 pounds heavier. Sigmoidoscopy on February 27, 1949, showed moderate congestion but no bleeding points, edema or ulceration. Aureomycin was decreased to 250 mg. daily.

CASE VII. E. G. was a male aged fifty. In February, 1946, following a cold, he had four to seven watery bowel movements a day, with blood and mucus. Since then, he has had frequent attacks of diarrhea with as many as fifteen to twenty movements a day. He believes the attacks of diarrhea are usually initiated by nervous tension. Repeated sigmoidoscopic examinations and barium enemas revealed typical findings of chronic ulcerative colitis.

About January 10, 1949, he had a cold and had six to eight bloody movements a day. Proctoscopy on January 21st revealed an ex-

four days the movements were reduced to six to eight and in the course of the following two weeks the bowel movements gradually diminished so that on February 15, 1949, he was having two or three formed stools a day. At this time aureomycin was discontinued for three days and the bowel movements promptly increased to five a day. When aureomycin was resumed (750 mg. daily), he again had two formed stools daily. There has been no change in the sigmoidoscopic picture.

CASE VIII. J. A., a female aged thirty-three, developed bloody diarrhea in March, 1943, and was hospitalized at the Mount Sinai Hospital for three months, receiving fifteen transfusions. Severe recurrence for five weeks in November, 1944, and again in February, 1947, necessitated hospitalization. When first seen on August 9, 1947, she was having six soft, bloody stools daily. Sigmoidoscopic examination was typical of ulcerative colitis, as was the roentgen examination which revealed, in addition, a complete situs inversus. Since the initial visit, she has had severe recurrences requiring further hospitalization, each recurrence lasting several weeks to

months. On February 12, 1949, there was a sudden onset of diarrhea with nine bloody movements daily. Aureomycin, 250 mg. every eight hours, was prescribed. Four days later the stools were reduced to four a day, without blood. This continued for ten days when the movements became formed and were only two in number. Between March 1st and 4th, she took no aureomycin and continued to feel well. On the latter date she began to menstruate; she also developed a cold and had six bowel movements. Aureomycin, 250 mg. every eight hours, was ordered and on each of the next two days she had eight bloody bowel movements. Aureomycin was increased to 500 mg. every eight hours with a gradual reduction in the bowel movements as well as a disappearance of blood. During the course of this episode the patient did not lose weight and sigmoidoscopic examination showed no change.

CASE IX. S. H. was a male aged forty-two. This patient had a duodenal ulcer with obstruction, for which a gastro-enterostomy was done in 1945. In November, 1948, he began having three soft, watery, frequently bloody bowel movements daily. Previously he had always had one or two formed movements. He attributed the diarrhea to increased nervous tension and worry over his son who was a mental problem. A barium colon enema and proctoscopy on December 4, 1948, were both positive for chronic ulcerative colitis. On December 8, 1948, aureomycin, 250 mg. every eight hours, was initiated. After one week the bowels became formed, were reduced to two daily and the blood became less and less until it was entirely absent. After six weeks aureomycin was reduced to 250 mg. twice each day with no alteration in bowel habits. Sigmoidoscopy on February 5, 1949, showed a few pin-point bleeding areas but no ulcers, edema, congestion or friability. Aureomycin was reduced to 250 mg. daily and on February 20, 1949, was discontinued. The movements continued to be formed, two daily (his previously normal bowel habit) and without any blood. During the time he was on aureomycin his weight increased from 161 to 165 pounds.

CASE X. R. R. was a female aged forty-four. In 1944 this patient had bloody diarrhea with fifteen to twenty movements daily, the attack lasting about four months. In November, 1948, she had twenty bowel movements each day for one month, which gradually became less, so

that for the next two months there were about ten stools a day containing much blood, pus and mucus. X-ray examination on February 15, 1949, revealed typical severe ulcerative colitis with polyp formation. Proctoscopy revealed profuse bloody purulent discharge, with an ulcerated, edematous and bleeding mucosa. The liver was 2 inches below the costal margin and tender, and there was marked edema of the ankles. She was hospitalized at the University Hospital (New York) where her temperature fluctuated up to 101°F. Laboratory study disclosed the liver function tests to be normal but marked anemia and hypoproteinemia were present (7.7 Gm. of hemoglobin; total protein 4.7 Gm.).

Aureomycin, 500 mg. every eight hours, was started and after one week the stools were reduced to four in twenty-four hours, all with less blood. At the end of the third week of treatment the patient had two formed movements daily, without blood, pus or mucus, and the ankle edema had subsided.

CASE XI. L. R. was a male aged forty-five. About five years ago this patient had an attack of diarrhea, cramps and fever lasting one week. In 1945 he had a recurrence of the diarrhea, with bleeding, which persisted to November 27, 1948, when he was first seen. His stools averaged five to six semisoft movements with varying amounts of blood, from specks to half teaspoonfuls. Preceding each movement there was a mucous discharge. Sigmoidoscopy revealed an edematous hyperemic mucosa which was the seat of geographic erosions. There was much bleeding with considerable lymphoid hyperplasia and mural fibrosis. Cultures were negative for *B. dysenteriae*. Aureomycin, 250 mg. every eight hours, was commenced on November 27, 1948. For two weeks he continued to pass some mucus and a little blood but no pus. The stools gradually became less frequent so that he had two or three formed movements daily without tenesmus, pus or blood. There was improvement in mood, he became brighter, more cheerful and less irritable. Sigmoidoscopic examination on December 11, 1948, showed an occasional pin-point bleeding area but no ulcerations. He continued to report further improvement and aureomycin was discontinued on February 15, 1949, after eleven weeks.

CASE XII. A. G. was a male aged thirty-two. In 1937 this patient began to have diarrhea while he was a student at college. The move-

ments fluctuated between four and twelve stools daily. He continued to have frequent bowel movements and was studied in 1941 and 1942 when barium enema showed an "extensive ulcerative colitis involving the entire large bowel." Similar findings were noted in later barium enemas and repeated sigmoidoscopies always showed typical ulcerative colitis findings. For the past several years he has averaged eight or nine soft bloody movements a day. Aureomycin, 250 mg. every eight hours, was started on December 22, 1948, and was continued four weeks with reduction of stools to five daily. At this time aureomycin was increased to 500 mg. twice daily. This produced no change in the stools but two weeks later the patient reported (by mail): "I now feel better than usual. The consensus is that I am looking well—for me."

Aureomycin was now dropped to 250 mg. every eight hours and two weeks later a similar report was received from the patient.

CASE XIII. C. C. was a female aged twenty-eight. For the past year this patient had from five to ten bowel movements daily containing blood and pus with tenesmus and urgency. Cramps were relieved by bowel movements. She was admitted to Harlem Hospital on January 15, 1949, where sigmoidoscopy showed an edematous and friable mucosa with small hemorrhagic areas and a purulent discharge. Barium colon enema revealed loss of haustration with diffuse irregularity of the outline of the descending colon. Aureomycin, 250 mg. every eight hours, was given on February 3, 1949, and was increased to 500 mg. every eight hours on February 8, 1949. The bowel movements were reduced to three daily, were more formed and contained less blood. Cramps continued and nausea developed. Aureomycin was reduced to 250 mg. every eight hours on February 19, 1949, and on this regimen she continued to have three to four soft bowel movements daily. Her weight dropped 12 pounds during the month. There was no change in the sigmoidoscopic picture.

CASE XIV. J. C. was a male aged thirty-eight. In this patient the onset of diarrhea was in 1931 with several attacks every year since. In 1935 blood was first noticed in the stool. Attacks recurred two or three times a year until 1939. From then on he was fairly well until 1945 when he had four to five bowel movements a day associated with considerable weight loss. In May, 1947, bowel movements increased to ten loose stools a day and this condition was ag-

gravated when he went away on a vacation. During the winter of 1947 to 1948 there was considerable diarrhea and he had "accidents" on the way to work so that he became quite nervous about going to his office. Repeated sigmoidoscopic examinations over these years revealed typical findings of chronic ulcerative colitis and a polyp 2 inches from the anus.

Aureomycin, 250 mg. every eight hours, was started on December 16, 1948. On January 17, 1949, he noted little improvement so the dose of aureomycin was increased to 500 mg. every eight hours. He remained on this regimen for three weeks after which he became so nauseated that he discontinued the drug. The bowel frequency was about the same (three to four) as before treatment but the stools were somewhat more formed and contained less blood. He felt stronger, had gained 5 pounds (115 to 120) and had had no "accidents," which heartened him a great deal.

CASE XV. H. C. was a male aged twenty-eight. In this patient the onset of diarrhea was in 1938, with frequent recurrences in 1940 and 1941, each with about eight or nine bowel movements a day. He was studied at the Roosevelt Hospital where a barium colon enema showed "atypical mucous membrane throughout the large bowel. There is definite ulceration of the transverse colon and descending portion." Although relatively well in the period of 1942 to 1947 there were occasional bouts of diarrhea, frequently with blood. Repeated sigmoidoscopic examinations revealed typical findings of ulcerative colitis. In September, 1947, he developed an ischiorectal abscess which required drainage and subsequent re-operation. During 1948 he averaged two semiformal bloody stools daily. Sigmoidoscopy on December 17, 1948, showed diffuse mucosal congestion with edema and many small bleeding points. Aureomycin, 250 mg. every eight hours, was given. On January 10, 1949, the patient stated that the stools had become very well formed although still containing slight blood. Sigmoidoscopy on this same date to 8 inches revealed normal mucosa. Aureomycin was reduced to 250 mg. twice daily. On February 4, 1929, bowel movements were well formed and numbered two daily containing somewhat less blood. Sigmoidoscopy again revealed normal mucosa. A weight gain of 8 pounds was noted.

A case of special interest, not included in this series, is reported from the Mount Sinai Hos-

pital. Aureomycin was requested by Dr. Burrill B. Crohn for use in treatment of one of his patients and an abstract of the protocol is as follows: A thirty-eight year old male (W. F.) entered the Mount Sinai Hospital on January 7, 1949. He had had recurrent exacerbations of chronic ulcerative colitis during the past twelve years. Three weeks before admission an acute exacerbation developed in which he had five to ten watery and bloody bowel movements daily accompanied by severe rectal tenesmus and fever. On admission he showed marked secondary anemia, a temperature of 102°F., pulse 100 and respiration 22. Laboratory studies revealed a hemoglobin of 12.9 Gm. This value varied according to transfusions and blood loss per rectum. The white blood count was 23,500 and the differential showed a shift to the left.

Under treatment with amphojel and deodorized tincture of opium he continued to have five or six watery bowel movements daily. From January 10th to the 19th he was given 2 Gm. of streptomycin daily in divided doses intramuscularly but despite this therapy his bowel movements averaged twenty daily. Bowel movements were foul in odor, containing pus, blood and mucus. On January 20th and 21st he was given 300,000 units of penicillin daily with no effect. On January 19th his condition had deteriorated showing abdominal distention and tenderness and spasm in the right lower quadrant associated with singultus and vomiting. A surgical consultant decided against surgical intervention and the patient was treated conservatively with nothing by mouth and a Harris tube. On January 21, 1949, it was deemed advisable to use aureomycin.

Treatment was initiated with intravenous administration of 600 mg. of aureomycin in divided doses and 250 mg. orally four times a day. The oral route was employed despite the fact that some of the drug would be lost through the Harris tube. At the beginning of treatment his temperature was 102°F., pulse 130 and abdominal distention was present with marked tenderness on the right side. Thirty-six hours later the temperature fell to normal but rose again to 101°F. on the fifth and sixth days after treatment was started. On the sixth day of aureomycin therapy the temperature fell to normal and remained normal thereafter. During this period there was a distinct change in the character of the bowel movements. On an average there were eleven bowel movements per day.

Some were semiformal, non-odorous, containing no pus and little or no blood. The color also changed from green to light yellow. On February 1, 1949, the patient was placed on oral aureomycin alone, receiving 250 mg. four times a day and his condition was definitely improved. At this time an ileostomy was decided upon and on February 3, 1949, it was carried out. Operation revealed "evidence of acute and chronic inflammation of the right lower quadrant with the terminal ileum adherent to the cecum. There was also an inflammatory process in the pelvis. These processes were probably due to a recent perforation." Postoperatively, the patient continued on intravenous aureomycin for the first forty-eight hours during which time he had the usual postoperative reaction. However, on the second postoperative day the temperature increased to 103.8°F. with a pulse to 134. Bowel movements became bloody, increased in frequency and the patient went rapidly downhill and expired on February 11, 1949.

RESULTS

The fifteen cases constituting this study may be divided into two groups: (1) Thirteen cases representing "active" colitis (i.e., diarrhea of from three to twenty-five bowel movements daily with typical sigmoidoscopic and roentgen findings) and a second group (2) of two cases (xiv and xv) which at the time of study were in a "quiescent" phase (although still displaying roentgen and sigmoidoscopic evidence of disease and with a history of repeated earlier bouts of severe activity).

Active Cases. Bearing this division in mind, it is immediately apparent that the greatest effect occurred in the diarrheal group (1) of which all thirteen patients showed a reduction in the number of daily stools. This reduction amounted to at least 50 per cent in eleven of the thirteen cases. The majority of cases (I, II, III, V, VII, VIII, X, XI and XIII) exceeded this reduction and were having one-third, one-fourth, or even fewer movements than before initiation of aureomycin.

There were two cases (of thirteen) in which stools were reduced but by less than one-half. In one of these (Case XII) the colitis

history extended twelve years and the movements had been "stabilized" at about nine daily. These were reduced in about four weeks to five per day. The second case (Case ix) was a colitis of brief duration (one month) with minimal symptoms, and the patient's bowel habit was restored to the "pre-colitic" normal (two) after one week of aureomycin.

Gross blood was present in the stools of all thirteen patients. As treatment progressed it disappeared completely from eleven (85 per cent) and was reduced in amount and/or frequency in the remaining two patients.

A change in the consistency of stools was also observed. All of the thirteen patients had watery or semiformal stools before commencing aureomycin therapy. Of these, ten (77 per cent) later had formed stools and in two more the stools became gradually firmer although never fully formed. Thus, concomitant with the reduction in diarrhea, twelve of the thirteen patients (92 per cent) developed improved consistency of the stools.

Along with the reduction of bowel movements there was a gain in weight in seven patients (of thirteen) ranging from 4 to 28 pounds. The patients displaying the most severe degree of nutritional deficiency manifested, in general, the greatest degree of recovery while those who had maintained their weight despite the disease showed only little (Case ix) or no improvement in this respect.

Two patients, although showing reduction in diarrhea, lost weight. In the first case (Case xii) this was in large part due to nausea which developed incident to use of the drug, the weight loss being promptly reversed when nausea was controlled by use of aluminum hydroxide gel. The second patient (Case x) lost about 3 pounds in the first two weeks of hospitalization, apparently due to disappearance of marked ankle edema, when the hypoproteinemia was relieved.

General well being kept pace with reduction in bowel movements and weight gain.

Practically all of the patients in this group said they felt much better and stronger.

Seven of twelve patients showed improvement in the sigmoidoscopic appearance. This took the form of reduction in congestion and edema, decrease in bleeding points and ulcers and less granular appearance of the mucosa. In some cases the sigmoidoscopic picture was normal.

The improvements reported were obtained in some of the patients within a week or two but often the maximum benefit was not achieved for three to five weeks or longer. Aureomycin was continued well beyond this time whenever possible so that the value of a prolonged course of antibiotic therapy could be determined.

Quiescent Cases. As was to have been expected the patients in the quiescent group (2) showed no change in the number of their bowel movements. But even here certain benefits were reported. Case xiv, a very undernourished thirty-eight year old male weighing 115 pounds, gained 5 pounds and stated that he felt better despite marked nausea which forced him to discontinue the drug. In addition, the stools had become more formed and he no longer had "accidents." There was no change in the appearance of the bowel on sigmoidoscopy. Case xv gained 8 pounds in weight, reported slightly less blood in the stools which had become well formed and showed some improvement in the sigmoidoscopic picture.

Toxic Effects and Side Reactions. No toxic effects or side reactions were observed in this series of cases other than nausea. This was noted in three of the fifteen patients. J. C. (Case xiv) became so nauseated after 1,500 mg. daily for three weeks that he had to discontinue the drug. Case xiii continued to take the drug despite marked nausea, which resulted in anorexia and weight loss. The nausea was controlled when aluminum hydroxide gel was administered simultaneously with aureomycin and the dosage of the drug was reduced.

Evaluation. The difficulty in determining the value of any therapy in ulcerative colitis is well known. No disease has more

of a tendency toward natural, spontaneous remission, often occurring suddenly just when the picture seems blackest. The powerful effect of psychologic influences, such as the exhibition of a new therapy, is also well known. The greatest caution must therefore be exercised in imputing a specific virtue to any therapy in this disease. We believe, however, that the high degree of response to aureomycin obtained in these unselected cases is encouraging and significant and deserves further study.

SUMMARY AND CONCLUSION

1. Thirteen patients with active ulcerative colitis were treated with aureomycin hydrochloride* in doses averaging 250 mg. every eight hours. All showed reduction in the number of bowel movements; in eleven of the thirteen cases (85 per cent) this reduction amounted to 50 per cent or more.

2. In eleven of the thirteen cases (85 per cent) the gross blood in the stools disappeared.

3. All of the thirteen active patients reported improvement in the sense of well being (including greater strength, less pain and tenesmus and cessation of accidents).

4. Gain in weight (4 to 28 pounds) was reported in seven patients (54 per cent) during treatment. Weight loss occurred in two hospitalized cases.

5. The sigmoidoscopic appearance was improved in seven of twelve patients.

* The aureomycin used was furnished through the courtesy of the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, N. Y.

6. Two patients with quiescent ulcerative colitis showed no change in daily bowel movements but reported improvement in well being, less blood in the stools and a weight gain of 5 and 8 pounds, respectively.

7. Severe nausea was experienced by three patients. This was controlled by aluminum hydroxide gel and reduction in dosage.

8. While the results herein reported are most encouraging and appear significant, great caution is urged in interpreting the value of aureomycin in ulcerative colitis therapy.

REFERENCES

1. BOCKUS, H. L. *Gastroenterology*. Vol. 2, p. 556. Philadelphia, 1944. W. B. Saunders Co.
2. PAULSEN, M. Present status of idiopathic ulcerative colitis. *J. A. M. A.*, 10: 1687, 1933.
3. FELSEN, J. Relationship of bacillary dysentery to distal ileitis, chronic ulcerative colitis, etc., *Ann. Int. Med.*, 10: 645, 1936.
4. HURST, A. F. Ulcerative colitis. *Guy's Hosp. Rep.* 85: 317, 1935.
5. BARGEN, J. A. Etiology of chronic ulcerative colitis. *J. A. M. A.*, 83: 332, 1924.
6. BOCKUS, H. L. The pathogenesis of idiopathic ulcerative colitis. *Delaware State M. J.*, 8: 1, 1936.
7. DUGGAR, B. M. Aureomycin: a product of the continuing search for new antibiotics. *Ann. New York Acad. Sci.*, 51: 177-342, 1948.
8. COLLINS, H. S. et al. Aureomycin—a new antibiotic. *Ann. Int. Med.*, 29: 9, 1948.
9. WRIGHT, L. T. et al. Aureomycin: a new antibiotic with virucidal properties. *J. A. M. A.*, 138: 408-412, 1948.
10. BRYER, M. S. et al. Aureomycin: experimental and clinical investigations. *J. A. M. A.*, 138: 117-119, 1948.
11. WRIGHT, L. T. and STRAX, S. Pyoderma gangrenosum in chronic non-specific ulcerative colitis treated with aureomycin. *Harlem Hosp. Bull.*, 1: 99-112, 1948.

Significance of Hyperalimentation in Treatment of Chronic Idiopathic Ulcerative Colitis^{*}

THOMAS E. MACHELLA, M.D.

Philadelphia, Pennsylvania

UNTIL two and one-half years ago our management of patients with chronic idiopathic ulcerative colitis, like that of many other clinics, consisted of: (1) a high caloric, low residue diet of which the patient ate very little; (2) a course of some sulfonamide, despite the fact that a pathogenic bacterium rarely, if ever, was isolated from the stool; (3) vitamins and (4) various antidiarrheal agents. When the patient failed to respond to these measures, he was referred to a surgeon for an ileostomy.

Then we tried a "medical ileostomy," the purpose of which is to place the colon at rest. This was accomplished by intubating the small intestine as far as the terminal ileum (or if the ileum was involved, to a point just proximal to the involved portion) with a Miller-Abbott tube and by applying constant suction so as to prevent the small intestinal contents from entering the diseased bowel. At the same time an effort was made to maintain the nutritional status of the patient by oral administration of a large quantity of a mixture of predigested casein and dextrimaltose in such solution that any residue could be withdrawn through the tube. The results were most satisfactory.

Our experience over a year with this procedure led us to suspect that the more effective factor in the improvement of the patient was the accomplishment of adequate nutrition by administration of the

hydrolysate-dextrimaltose solution. Therefore in a subsequent series of cases we omitted the intubation but retained all the other features of the adopted management: administration of an excessive amount of a readily absorbable dietary solution, high in protein and with added vitamins, blood transfusions when indicated and measures for the control of emotional disturbances. Chemotherapeutic agents and antibiotics were rarely employed.

Our experience with fourteen patients who had chronic non-specific ulcerative colitis so treated, compared with that of a series of patients who underwent intubation, comprises the basis of this report.

PROCEDURE

The patient was placed on a dietary regimen that consisted solely of administration of a solution of a mixture of equal parts of an enzymatic casein hydrolysate^{*} and of dextrimaltose. A measured amount of the mixture, sufficient for a day's feedings and calculated on the basis of 20 calories per pound of pre-illness weight, was dissolved in enough boiling water to yield a 15 to 25 per cent solution and stored in quart milk bottles in an ice chest. Two hundred to 400 cc. of the solution were ingested every two hours from 6 A.M. to 10 P.M., thus supplying 225 to 450 Gm. of protein and 1,800 to 3,600 calories daily. In addition the patient received iron and the following vitamin

^{*}The powder mixture, consisting of 50 per cent protolysate and 50 per cent dextrimaltose No. 2, was generously supplied by Mead Johnson and Co.

^{*}From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

supplements by mouth: thiamine, 10 mg., nicotinamide, 100 mg., riboflavin, 2 mg. and ascorbic acid, 50 mg. three times per day and 1 multivitamin capsule and 2 mg. of vitamin K daily. Administration of the solution was continued until such time as clinical and sig-

half months pregnant. The terminal ileum, in addition to the colon, was involved in four patients.

The average loss of weight prior to the onset of therapy was 20 (6 to 34) pounds, and the number of stools ranged from an average

TABLE I
DESCRIPTION OF PATIENTS

Case No.	Sex/ Age	Duration *		General Physi- cal Ap- pear- ance	Fever	Ano- rexia
		Of Disease	Of Im- mediate Attack			
1	M/13	2 Y*	2 M	Critical	+	+
2	M/29	2 Y	3 M	Good	0	+
3	F/60	4 Y	7 M	Good	0	+
4	F/21	19 M*	6 M	Good	0	0
5	M/25	11 Y	1 M	Good	+	0
6	M/22	8 Y	4 Y	Poor	+	+
7	M/60	4 Y	4 Y	Poor	+	+
8	M/30	2 Y, 9 M	7 D*	Good	0	0
9	M/50	2 Y	2 Y	Good	+	+
10	M/50	3 M	3 M	Good	+	+
11	F/32	18 M	18 M	Good	+	0
12	F/38	1 M	1 M	Good	0	+
13	M/31	5 Y	3 M	Poor	0	+
14	F/29	5 Y	1 Y	Good	0	0

* Y = years, M = months, D = days

midoscopic improvement was observed. Then increasing amounts of a high caloric, high protein and low residue diet of the ordinary type were ingested and the hydrolysate-dextrin-maltose solution was correspondingly reduced.

Other abnormalities, such as hypochloremia, acid-base imbalance and dehydration, if present, were corrected as promptly as possible. Anemic patients received transfusions of whole blood. Emotional disturbances were given special attention, the psychiatrists being called in when their services seemed to be indicated.

Description of Patients. The fourteen cases represent thirteen patients, one of whom had a relapse. They were fairly representative of the types of disease usually encountered. (Tables I, II, III and IV.) Some cases were acute and others chronic but all were regarded as being severe. Seven of the patients had varying degrees of fever, ranging from a low grade pyrexia to the more severe forms such as occur in the fulminating types of the disease. One patient (Case XIII) had erythema nodosum and acute arthritis; another (Case XII) was three and one-

TABLE II
PROCTOSIGMOIDOSCOPIC FINDINGS AND EXTENT
OF INVOLVEMENT AS DETERMINED
ROENTGENOLOGICALLY

Case No.	Sigmoidoscopic Findings			Part of Intestinal Tract Involved According to Roentgen Examination
	Hyper- emia	Edema	Ulcers	
1	Patient too ill; not examined			Entire colon and ter- minal ileum
2	+	0	+	Entire colon
3	+	+	0	Sigmoid
4	+	0	0	Entire colon
5	+	+	+	Descending colon and sigmoid
6	+	+	+	Entire colon and ter- minal ileum
7	+	+	0	Descending colon and sigmoid
8	+	+	0	Entire colon
9	+	+	0	Entire colon
10	+	0	0	Cecum and sigmoid
11	+	+	0	Entire colon and ter- minal ileum
12	+	+	0	Sigmoid
13	+	+	0	Entire colon and ter- minal ileum
14	+	+	0	Entire colon

TABLE III
CHANGES IN BODY WEIGHT IN POUNDS

Case No.	Before Onset of Illness	At Onset of Treatment	On Discharge from Hospital	On Recent Follow-up
1	90	58	78	107
2	180	150	159	162
3	152	143	143	152
4	105	80	85	109
5	164	147	150	158
6	136	106	104	118
7	175	141	145	151
8	162	152	153	165
9	136	116	120	136
10	200	181	185	187
11	138	108	104	112
12	137	124	124	122
13	121	115	109	116
14	167	152	Still in hospital	

minimum of 6 to an average maximum of 11.1 per twenty-four hours.

The duration of strict hydrolysate-dextrin-maltose therapy alone averaged 24.4 (seven to sixty days). The patients were hospitalized an average of 32.7 (11 to 70) days after beginning

subjected to severe emotional insults. The fever subsided when a bad domestic situation was corrected and has not returned.

Anorexia. After seven to fourteen days of therapy anorexia was replaced by appetite and subsequently by hunger. A

TABLE IV
CHARACTERISTICS OF STOOLS PRIOR TO THERAPY AND ON DISCHARGE FROM HOSPITAL

Case No.	Prior to Therapy				On Discharge from Hospital			
	No. of Stools per 24 Hours	Character			No. of Stools per 24 Hours	Character		
		Consistency	Blood	Mucus		Consistency	Blood	Mucus
1	8-12	L*	+	+	7-8	SF	+	+
2	6-32	L	+	+	1-2	F*	0	0
3	1-2	SF*	+	+	1	F	0	0
4	3-5	SF	0	+	1-2	F	0	0
5	6-8	L	+	+	2-4	F	0	+
6	6-7	L	+	+	0-1	F	0	0
7	10-15	L	+	+	1-2	F	0	0
8	5-6	L	+	+	5-6	L	0	+
9	10-12	L	0	+	1-2	F	0	0
10	3-4	L	+	+	0-1	F	0	0
11	6-8	L	0	+	1-2	F	0	0
12	8-30	L	+	+	1-2	F	0	0
13	4-5	L	+	+	1-2	F	0	0
14	8-10	L	+	+	1-2†	SF	+	0

* L = liquid; SF = semi-formed; F = formed

† Still in hospital

the special form of therapy. (Table v.) The private patients in the series (Cases II, VIII, IX and XII) were not kept in the hospital as long as was desirable because of the expense of hospitalization. One of them (Case VIII) continued the hydrolysate therapy at home.

RESULTS

General. Within seven to fourteen days of the institution of the therapy, an improvement in the general condition of the patient usually occurred. This was reflected in his subjective feeling as well as in his appearance and in a return of appetite.

Fever. Fever subsided without the use of sulfonamides or antibiotics in six of the seven patients. In one instance (Case I) sulfasuxidine was administered and appeared to abolish the pyrexia. In another (Case X) the fever relapsed when the patient was

complaint of hunger was the most reliable sign heralding the patient's subsequent improvement. Stigmas of vitamin deficiency (cheilosis and glossitis) present on admission in two patients (Cases I and II) disappeared.

Body Weight. During the period of liquid alimentation most of the patients maintained or gained weight. Some of this was due to retained fluid since loss of weight and diuresis usually occurred when the transition to an ordinary diet was first made. Maximal weight gain was not attained until a high caloric and low residue, but otherwise normally mixed diet, was ingested, especially after the resumption of home-cooked food. The average gain in weight was 3 pounds (-6 to 20) at the time of discharge from the hospital, and at the time of the latest follow-up, 13.4 pounds (-2 to 49). (Table III.)

Stools. When the liquid dietary regimen was instituted, the number of stools per day promptly decreased, remained the same or, in a few instances, increased. A sharp increase in the number of rectal discharges indicated that either some situation had arisen which had upset the patient

TABLE V
DURATION OF THERAPY

Case No.	No. of Days Hydrolysate and Dextrimaltose Were Only Source of Calories	Total No. of Days in Hospital
1	31	41
2	20	21
3	7	11
4	19	37
5	56	70
6	30	40
7	23	25
8	7	13
9	10	14
10	28	40
11	14	23
12	16	21
13	60	70
14	30	Still in hospital

emotionally, that the concentration of the solution was excessively hypertonic or that the solution had become contaminated with bacteria. Respite from the emotional upset or correction of the abnormality in the diet consistently resulted in a reduction in the amount of diarrhea.

The most consistent and striking decrease in the number of stools occurred when the patient was again placed on an ordinary high caloric, low residue and bland diet. The stools also became formed. At the time of discharge from the hospital (Table IV) the number of stools varied from an average minimum of 1.6 to an average maximum of 2.6 per twenty-four hours. The two patients (Cases I and VIII) who had five to eight stools per day at the time of discharge from the hospital were permitted to leave before complete remission was induced. A decrease in the number of stools occurred subsequently as they continued to improve.

Proctosigmoidoscopic Appearance. Prior to the onset of therapy the most frequent

proctosigmoidoscopic appearance was that of hyperemia, edema and, on passage of the scope or light wiping, a tendency to bleed. (Table II.) Actual ulcerations usually were not seen until the edema had subsided, at which time they were seen in all patients examined.

TABLE VI
FOLLOW-UP DATA

Case No.	Duration of Remission (mo.)	Weight Gain Since Discharge from Hospital (lbs.)	No. of Stools per 24 Hours	Ability to Resume Pre-illness Status
1	17+	29	2-3	+
2	9*	3	1-2	+
3	15+	9	1	+
4	13+	24	1	+
5	8+	8	2-3	+
6	8+	14	1-2	+
7	8+	6	2-3	+
8	6+	12	3-4	+
9	5+	16	1-2	+
10	4+	2	0-1	+
11	4+	8	2-3	+
12	2½+	-2	1-2	+
13	1+	7	3-4	Convalescing
14		Still in hospital		

* Relapsed; data refer to status immediately prior to relapse.

The improvement in the proctoscopic appearance was the form of objective evidence that appeared to parallel the clinical course of the patient most closely. At the time of discharge from the hospital the status of the involved lower bowel was reported as "healed" in one case (Case III), "no change" in one (Case VIII) and "improved" in ten. One patient (Case I) was not proctoscoped because of marked apprehension. Five of the ten patients who were considered improved at the time of discharge have been reported as healed at subsequent examination. It has not been possible to examine proctoscopically the remainder, but clinically they are now in remission.

Roentgen Appearance of the Colon. Improvement in the roentgen appearance of the colon usually lagged behind that observed

clinically and sigmoidoscopically. In only one of the patients (Case XII) was the colon reported to be normal at the time of discharge from the hospital. In the remainder the appearance by barium enema was reported as no change or improved. Follow-up barium enema studies were per-

comparable to those of the group that were treated without intubation, with certain exceptions. The intubated group had lost more weight (an average of 11 pounds) and, in contrast to one such patient in the latter group, included four patients with the severe fulminating type of the disease.

TABLE VII
COMPARISON OF CLINICAL CHARACTERISTICS AND DURATION OF THERAPY IN INTUBATED AND NON-INTUBATED PATIENTS

	Intubated	Not Intubated
No. of cases.....	12	14
Age in years.....	11 to 58	13 to 60
Duration of disease.....	1 M to 15 Y	1 M to 16 Y
Duration of attack treated.....	26 D to 9 M	7 D to 4 Y
Apparent psychogenic motivation.....	11	14
No. with fever.....	8	7
No. with fulminating type.....	4	1
No. of stools per 24 hours	2 to 25 (7.7 to 13.8)*	1 to 32 (6 to 11.1)*
Loss of weight.....	31* (10 to 98)	20* (6 to 34)
Terminal ileum involved in.....	3	4
Duration of liquid diet in days.	26.1* (5 to 52)	24.4* (7 to 60)
No. of days in hospital..	52.5* (5 to 126)	32.7* (11 to 70)

* Average

formed when possible. These revealed either progressive improvement or no detectable change.

Relapses and Follow-ups. (Table VI). A satisfactory remission was induced in all of the fourteen patients. A relapse occurred in one. (Case II.) It occurred when he learned that he was to be transferred to another section of the country shortly after he had purchased and moved into a new home. The relapse occurred after nine months of freedom from symptoms of colitis and of useful employment. A remission has again been induced. (Case VIII.)

Intubation. The clinical, sigmoidoscopic and roentgen characteristics of the group of twelve patients (Tables VII, VIII and IX) that were subjected to intubation were

TABLE VIII
COMPARISON OF RESULTS IN INTUBATED AND NON-INTUBATED PATIENTS AT DISCHARGE FROM HOSPITAL

	Intubated (12 cases)	Not Intubated (14 cases)
Satisfactory clinical remission.....	11	14
Deaths.....	1	0
No. of stools per 24 hours.....	0 to 6 (1.7 to 2.8)*	0 to 8 (1.6 to 2.6)*
Weight gain.....	8.2* (0 to 16)	3* (-6 to 20)
Sigmoidoscopic opinion	<div> healed..... 3 improved..... 7 no change..... 0 no involvement..... 1 not examined..... 0 </div>	<div> 1 10 1 0 2 </div>

* Average

TABLE IX
COMPARISON OF RESULTS IN INTUBATED AND NON-INTUBATED PATIENTS ON MOST RECENT FOLLOW-UP

	Intubated (12 cases)	Not Intubated (14 cases)
Relapses.....	3 (7, 9, and 13 M) 15.6 M*	1 (9 M) 8.2 M*
Duration of remission in non-relapsed patients.....	(5 to 23 M)	(1 to 17 M)
No. able to resume pre-illness duties.....	11	12†
No. of stools per 24 hours.....	0 to 6 (1.2 to 3)*	0 to 4 (1.5 to 2.2)*
Weight gain.....	16* (0 to 34)	13.4* (-2 to 49)
Sigmoidoscopic opinion	<div> healed..... 7 improved..... 0 no involvement..... 1 not examined..... 3 </div>	<div> 6 2 0 6 </div>

* Average

† Two patients still convalescing; one at home and the other in the hospital

The period during which the liquid diet was administered was similar in the two groups although the intubated group spent more time in the hospital. One of the reasons for this was the fact that four of the patients in the non-intubated group were private patients and, because of the expense, were hospitalized for a shorter time.

The follow-up results are quite comparable in the two groups. Three in the intu-

bated group have had relapses as compared to one in the other group, but the follow-up period for them was seven months longer. More of the non-intubated patients may relapse as time goes on. At present all of the patients in both groups are clinically well. Only two, and they of the more recently treated patients in the non-intubated group, have not as yet resumed their pre-illness employment status; one is convalescing at home and the other has not left the hospital.

COMMENT

The foods of the usual diet are not satisfactory in the management of idiopathic ulcerative colitis during the stage of acute inflammation for various reasons: The average patient has already become malnourished with such a diet available to him and is in negative nitrogen balance. Even if consumed in adequate amounts, Elsom, Dickey and Chornock² have shown by study of the nitrogen content of the ileal discharges in four of seven severely ill patients, the protein fraction of the usual diet is poorly absorbed. That portion we now know is essential for the repair of damaged tissue such as occurs extensively in this disease. Also, on the basis of physiologic experiments, it is clear that the residue of the ordinary diet as it passes into the colon induces active peristalsis, even mass movements.

On the other hand, the casein hydrolysate-dextrimaltose solution seems advantageous for nutrition of the colitis patient for the following reasons: (1) It permits a large protein and calory intake; (2) it supplies the protein in a readily absorbable form (Emery and McGee);³ (3) it tends to convert a negative into a positive nitrogen balance; (4) it has little if any residue, thus preventing undue irritation of the diseased colon.

Certain practical difficulties, however, are encountered in using such alimentation as the sole source of calories. The patient must be willing to subsist on the solution and continue its ingestion until objective

evidence of healing occurs. Some dislike it at first because of its unpalatable taste; however, the average patient becomes accustomed to it in about two days. At times, particularly at the onset of therapy, it may be necessary to adjust the concentration of the solution. If too concentrated, it remains in the stomach until diluted sufficiently by gastric juice. Under such conditions subsequent feedings, administered at two-hour intervals, may be retained until gastric fullness, nausea and vomiting occur. When this happens, the patient is instructed to omit the next feeding until sensations of nausea and gastric fullness have disappeared and to follow the subsequent feedings with a glass of water to shorten the period of retention in the stomach. The next day the solution is made up and administered in less concentrated form. The solution itself may give rise to diarrhea if it finds its way into the intestine in hypertonic form or if it becomes contaminated with bacteria. This latter occurrence can be detected by the loss of its clear appearance. However, if the milk bottles are sterilized and when filled are put in the refrigerator, this does not occur. It is important to use a hydrolysate preparation which dissolves completely. If it fails to do so, it should not be used. The patients are permitted water as desired as well as hard candy to get rid of the taste of the solution.

Included in management of the patients is an attempt to discover and successfully to handle the emotional problems which appear to be important in the motivation of the disease. All of our patients (with the possible exception of one who was allergic to dairy products) were tense, high strung, exacting, apprehensive and hyperreactors to emotional disturbances. In some instances the rapidity of response appeared to be directly proportional to our success in helping the patient readjust himself to a bad situation. Following discharge from the hospital, the patients are followed when possible at regular and frequent intervals and are encouraged to return for observation at any time when threatening situations

arise. In a number of instances it is believed that relapses were thus aborted. The patient as well as the disease must be treated.

In view of our satisfactory results with the hyperalimentation regimen of therapy in non-intubated patients it is planned to reserve medical ileostomy for special patients, such as those with excessive small intestinal hypermotility, those with threatened perforation, those with tenesmus from an inflamed and irritated rectum and those in whom the diarrhea does not subside when the hyperalimentation method alone is employed.

SUMMARY

The results obtained in the treatment of fourteen cases (thirteen patients) of chronic idiopathic ulcerative colitis by a plan of hyperalimentation are presented. The method permits ingestion of a large number of calories and a large amount of protein in readily assimilable form and with little residue. This is accomplished by oral administration of a solution of equal parts of an enzymatic casein digest and of dextrimaltose. After varying periods of time the amount of the solution is reduced and gradually increasing amounts of substantial foods, low in residue, are ingested. Essential vitamins and iron are added.

Objective evidence of improvement con-

sists of cessation of fever, disappearance of anorexia and of the stigmas of vitamin deficiency, return to normal in the number and character of the stools and gain in weight and in sigmoidoscopic evidence of improvement in the diseased portion of the bowel.

A satisfactory remission was induced in all of the fourteen patients treated. A relapse occurred in one patient after nine months of freedom from the symptoms of colitis.

The results are compared with those obtained in patients who were subjected for a temporary period to a medical ileostomy. Except for minor differences, the end results are quite similar.

The use of medical ileostomy has not been abandoned but is reserved for special cases since the regimen just described seems to be effective in most uncomplicated cases.

REFERENCES

1. MACHELLA, T. E. and MILLER, T. G. Treatment of idiopathic ulcerative colitis by means of a "medical ileostomy" and an orally administered protein hydrolysate-dextrimaltose mixture. *Gastroenterology*, 10: 28, 1948.
2. ELSOM, K. A., DICKEY, F. G. and CHORNOCK, F. W. Functional disturbance of the small intestine in chronic idiopathic ulcerative colitis. *Am. J. Digest. Dis.*, 9: 74, 1942.
3. MCGEE, L. C. and EMERY, E. S., JR. Rate of absorption of amino acids from the small intestine in man. *Proc. Soc. Exper. Biol. & Med.*, 45: 475, 1945.

Chronic Gastritis*

A Study of Symptoms and Gastric Secretion

JOHN W. FINDLEY, JR., M.D., JOSEPH B. KIRSNER, M.D., WALTER LINCOLN PALMER, M.D. and
THEODORE N. PULLMAN, M.D.

Chicago, Illinois

A LARGE literature concerning chronic gastritis has accumulated since the appearance in 1937 of Schindler's valuable book on gastroscopy. The role of gastritis in the production of symptoms, however, remains a controversial topic. Schindler has wisely stated, "The surest approach to the problem of symptoms would be the statistical approach."¹ Using such a method we have endeavored to answer the following questions: (1) Does chronic gastritis cause symptoms? (2) If so, do the three commonly recognized types of gastritis (atrophic, superficial and hypertrophic) produce specific symptoms? (3) What is the pattern of hydrochloric acid secretion following the injection of histamine in persons with chronic gastritis as compared with individuals with normal mucosae?

METHODS AND RESULTS

Symptoms. Four groups of patients were studied: (1) Fifty patients with atrophy of the gastric mucosa; (2) fifty with superficial gastritis; (3) fifty with hypertrophic gastritis and (4) a control group of one hundred individuals whose gastric mucosae appeared normal. All patients underwent gastroscopy because of digestive complaints. The absence of other organic disease was established insofar as possible by the clinical history, physical examination, blood counts, urinalyses, blood serologic tests and x-rays of the upper gastrointestinal tract in all of the 250 patients. Barium enemas were performed in 218 and cholecystograms in 137; all were normal. Proctoscopic examinations

and benzidine tests for occult blood in the stools were carried out in nearly all patients and were essentially negative. The patients were selected simply on the basis of unequivocal gastroscopic findings and adequate diagnostic investigation. Among those with gastritis the *minimum* requisites for inclusion in the study were either moderate to marked changes involving at least one-third of the stomach or mild, extensive gastritis. The only symptoms considered were those elicited before gastroscopy so that none were brought out in the light of the gastroscopic findings.

The results of the symptomatic survey are tabulated in Table I. Pain and distress were partially separated. Distress was taken to signify any abdominal discomfort other than pain. Arbitrarily, if "distress" was an important or the only complaint, it was tabulated but if it was mentioned merely as a mild accompaniment of pain, the pain was listed without the addition of "distress." In a few instances both were prominent enough to warrant recording.

It will be noted that "weakness" has been listed. This is a difficult symptom to evaluate but was included because it has been attributed to atrophy of the gastric mucosa.²

The symptoms apparently did not vary significantly among the four groups. Three per cent of the control group and 4 per cent of those with superficial gastritis had no pain or distress while 14 and 18 per cent of those with hypertrophic gastritis and atrophy, respectively, had none. Abdominal pain, the most frequent complaint, showed little difference in incidence, occurring in 64 per cent of those with atrophy and hypertrophic

* From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago, Chicago, Ill.

gastritis, in 78 per cent of the superficial gastritis group and in 79 per cent of the controls; it was present in the epigastrium (the most common location) in from 44 per cent of the patients with atrophy to 72 per cent of the controls. Generalized abdominal pain occurred in 24 per cent of the group with atrophy and in 11 to 12 per cent of the

others. Burning pain was described most frequently by the control subjects; cramp-like pain was most common among the individuals with atrophy, but the differences are not striking. Antacids, milk and food were slightly less effective in the relief of pain in persons with atrophy than in members of the other three groups. The time of

TABLE 1

SYMPTOMS ENCOUNTERED; EXCEPT FOR THE TWO TOP ROWS THE FIGURES REPRESENT PERCENTAGES

	Atrophic	Superficial	Hypertrophic	Normal
No. of patients.....	50	50	50	100
Average age.....	52	44	42	42
No pain or distress.....	18	4	14	3
Pain.....	64	78	64	79
Distress.....	20	20	22	28
Location:				
Epigastrium.....	44	68	62	72
Generalized.....	24	12	12	11
Low.....	8	2	10	5
Back.....	6	6	8	9
Type:				
Fullness.....	22	26	28	25
Burning.....	14	18	14	28
Gnawing.....	4	6	6	9
Sharp.....	8	10	2	5
Dull.....	6	16	20	19
Cramp-like.....	16	8	4	7
Soreness.....	4	4	4	8
Not described.....	12	8	16	10
Relieved by:				
Antacids.....	12	24	24	24
Milk.....	4	8	8	9
Food.....	12	18	24	18
Belching.....	12	16	12	9
Vomiting.....	4	2	0	2
Defecation and/or flatus.....	16	20	16	11
Heat.....	2	4	4	1
Rest.....	4	4	4	3
Time of occurrence				
Immediately after meals.....	20	12	16	20
An interval after meals.....	34	40	50	36
Awakening at night.....	14	12	14	8
Constant.....	12	16	16	9
No pattern.....	16	16	8	26
Nausea.....	32	24	24	32
Vomiting.....	12	10	14	14
Hematemesis.....	0	2	6	0
Anorexia.....	22	18	16	14
Constipation.....	32	26	20	33
Diarrhea.....	22	4	10	12
Melena.....	4	6	6	1
Weight loss.....	30	40	26	32
Weakness.....	20	18	12	14
Insomnia.....	4	0	0	3
Bad taste.....	4	2	2	2
Sore tongue.....	4	2	2	1
Numbness or tingling.....	6	2	0	1

occurrence was remarkably constant among the four groups. The discomfort was noted following a distress-free interval of twenty minutes to four hours after meals in 50 per cent of the hypertrophic gastritis group, 40 per cent of those with superficial gastritis,

exclude patients with other organic disease none was included who had persistently positive benzidine tests for occult blood in the stools.

Secretion. It was possible to determine quantitatively the gastric secretory response

TABLE II
ACID SECRETION; FASTING SPECIMENS ARE NOT INCLUDED

	Atrophic	Superficial	Hypertrophic	Controls
No. of patients	33	26	29	77
Average total mg. HCl. . . .	122	295	369	349
Average total volumes.	96	137	152	136
Average units free HCl. . .	23	49	60	66

36 per cent of the normals and 34 per cent of patients with atrophy. Distress immediately after eating was noted in 12 to 20 per cent of all the subjects; in 9 to 16 per cent the pain or distress was said to be constant; 8 to 14 per cent were awakened at night. No particular pattern was described by 8 per cent of patients with hypertrophic gastritis, 16 per cent of those with superficial gastritis or atrophy and 26 per cent of the controls.

Diarrhea occurred in 22 per cent of patients with atrophy as compared with 4 to 12 per cent of the other groups. Numbness or tingling of the extremities was reported by 6 per cent of patients with atrophy of the gastric mucosa and in 0 to 2 per cent of the remaining subjects. There were essentially no differences in the incidences of nausea, vomiting, anorexia, constipation, weight loss, weakness, bad taste or sore tongue. This was also true of the duration of symptoms and the degree of weight loss.

A history of hematemesis was given by 6 per cent of patients with hypertrophic gastritis, 2 per cent with superficial gastritis and by none of the remaining groups. Melena was described by 4 to 6 per cent of patients with gastritis and by one of the controls. However, the figures on bleeding may be misleading for, in order to eliminate from the study persons with weakness due to anemia, all who had red blood counts below 4 million or hemoglobin values below 12 Gm. were excluded. Furthermore, to

to histamine in 165 patients, measuring the total mg. of free hydrochloric acid, total volume and average units of free acid, as indicated in Table II. There was little average difference in total acid secretion between individuals with hypertrophic gastritis and the control subjects during the hour after subcutaneous injection of histamine. The average total mg. and the average total volumes were slightly higher in the hypertrophic gastritis patients but the average units of free acid were higher in the normals and none of these differences appears clinically significant. Although the average volume of secretion in the patients with superficial gastritis fell within the range of the hypertrophic gastritis group and the controls, the average acid output was less even though two of this group secreted very large amounts of acid. (Fig. 1.) Patients with atrophy of the gastric mucosa secreted the smallest amounts of acid. The range of acid output was found to be very wide, the highest secretor being a patient with superficial gastritis who produced 1,277 mg.

When the differences among the means of total mg. of acid secreted were evaluated from a statistical point of view, highly significant differences were found between the group with atrophy and the controls, and between the groups with atrophy and hypertrophic gastritis. The difference in total mg. between the superficial gastritis and atrophy groups also is significant. A

statistical analysis of the differences between the means of total volumes and clinical units of free hydrochloric acid also indicated significant differences when the same comparisons were made. Other differences could not be proved to be significant.

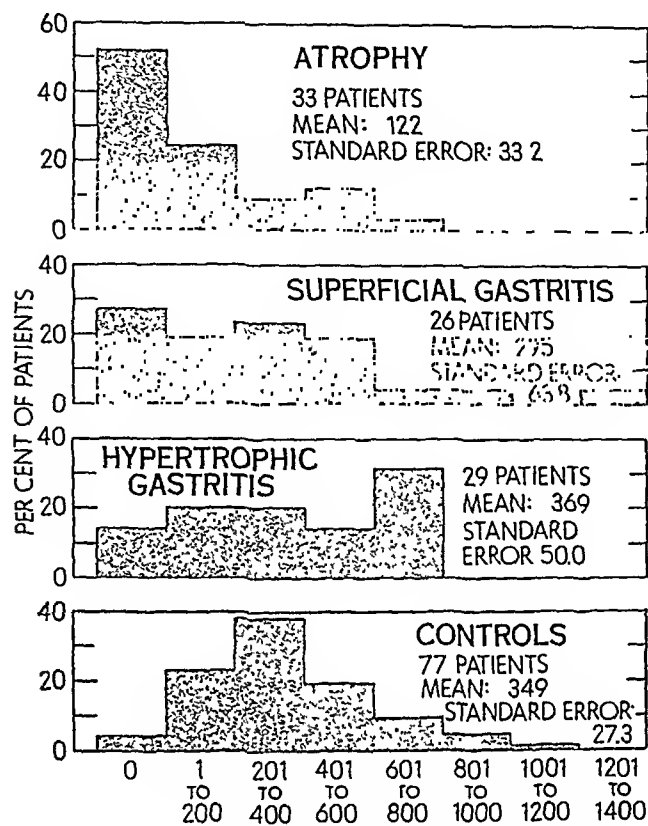


FIG. 1. Distribution of total mg. of hydrochloric acid secreted during one hour after injection of histamine.

The distribution of patients secreting a total of more than 600 mg. of acid in response to histamine was compared by use of an exact formula for calculating probabilities, employing a four-fold table.³ The proportion of individuals with hypertrophic gastritis who secreted more than 600 mg. was significantly greater than that of persons with normal mucosae or with atrophy. The present data indicate that similar hypersecretion occurs more commonly in normals than in persons with atrophy, and more often in those with hypertrophic gastritis than in persons with superficial gastritis. However, the probability that this distribution could occur entirely due to chance errors was found to be approximately 0.06 when assayed by this method. This figure is slightly greater than the usually accepted upper limit of statistical significance, 0.05.

No significant difference could be proved to exist in this regard between the control and superficial gastritis groups nor between the atrophic and superficial gastritis groups.

The incidence of anacidity after histamine (Fig. 2) was 52 per cent of thirty-three

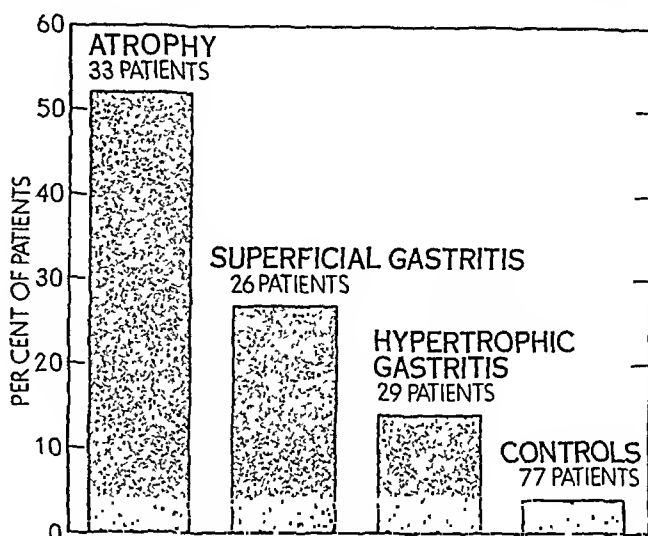


FIG. 2. Incidence of histamine anacidity.

patients with atrophy of the gastric mucosa, 27 per cent of twenty-six with superficial gastritis, 14 per cent of twenty-nine with hypertrophic gastritis and 4 per cent of seventy-seven controls. In this series the differential incidence between patients with atrophy and controls and between individuals with superficial gastritis and the same control group was found to be statistically highly significant. However, in the comparison between the hypertrophic gastritis group and the controls chance alone could have accounted for the distribution 7.1 times in one hundred, as estimated by use of the aforementioned four-fold table.

COMMENTS

Symptoms. The answers which these data offer to the questions posed in the introductory paragraph are for the most part not categorical. Since all patients had complaints that led to gastroscopic examinations, they do not represent a cross section of the general population and the control group is not truly a "normal" group. Indeed, unless this is kept in mind it might at first seem unusual that such a high percentage of the patients with normal mucosae had epi-

gastric pain. The greatest variations from group to group occurred in the incidences of epigastric pain (44 per cent among patients with atrophy to 72 per cent among the normals) and of diarrhea (22 per cent of patients with atrophy compared with 4 to 12 per cent for the other groups). These differences appear to be of uncertain significance.

The incidence of gastritis in patients with dyspepsia has been found to be 42 to 44 per cent.⁴⁻⁶ The incidence in patients of similar ages without symptoms is not known precisely. The beginning of a series designed to explore this problem was reported by Fitzgibbon and Long⁷ who found that thirty-eight of forty healthy young adult males had a normal-appearing mucosa; the remaining two had hypertrophic gastritis. A similar investigation consisted in the gastroscopic examination of thirty-three volunteers with an average age of twenty-five years.⁸ All were normal except three who had mild, patchy atrophy of the gastric mucosa. Ruffin and Brown examined thirty-two students having no complaints and found normal mucosae in all instances except five, in which only hemorrhagic or pigment spots were seen.⁹ Thus, chronic gastritis was observed in only 5 of 102 young asymptomatic volunteers.

Two groups of young subjects with dyspeptic symptoms referred to the upper abdomen were studied gastroscopically during World War II. All had normal gastroduodenal x-rays. One group was composed of 110 soldiers near a battle area in Italy.¹⁰ Redness and edema of the gastric mucosa were noted in twenty-nine, unequivocal superficial gastritis in sixteen and hypertrophic gastritis in two. The preponderance of superficial changes was chiefly attributed to the unusually high degree of anxiety manifested by these patients. In the other group consisting of eighty-three soldiers in the United States only ten instances of hypertrophic gastritis, atrophy or mixed hypertrophic gastritis and patchy atrophy were found.¹¹ Although the former group was in a sense selected, and despite the fact

that gastroscopic interpretations vary, these findings appear to lend support to the thesis that abnormalities of the gastric mucosa are more common among persons with abdominal complaints than among asymptomatic persons. The more advanced ages of persons with atrophy, as exemplified by our data, suggests an explanation for the low incidence of atrophy in the soldiers.

Gray gastroscoped one hundred chronic alcoholics in an effort to determine the effect of alcohol on the gastric mucosa.¹² After noting the gastroscopic findings he interrogated them regarding symptoms. "Only 4 of 55 patients with normal or essentially normal stomachs had mild abdominal and epigastric distress, while 24 of the 45 patients with chronic gastritis presented definite subjective complaints." Symptoms were present in twelve with superficial gastritis, including two in whom the distress was ulcer-like; ten with the same type of gastritis were symptom-free. Of the patients with atrophy twelve had symptoms, including four who complained only of profound weakness; the remaining nine were asymptomatic. The two patients with hypertrophic and hyperplastic nodular gastritis did not have symptoms. No statements were made regarding the ages of these subjects, nor was there mention of x-rays, blood counts or other studies to exclude the possibility of other organic disease.

Schindler has concluded that the common types of chronic gastritis are usually characterized by distinctive symptoms.¹ The patient with superficial gastritis is considered to have one outstanding complaint: epigastric pain, usually moderate and vague but sometimes constant; nausea, anorexia, weight loss, weakness and diarrhea may occur. Atrophy of the gastric mucosa is thought to produce "an entirely different picture"; the syndrome changes if the superficially inflamed gastric mucosa becomes atrophic. Although epigastric distress is usually present, this is of secondary importance to profound weakness and fatigue, often associated with anorexia and weight loss. Paresthesias, numbness and tingling

of the extremities and soreness of the tongue are said to be frequent. Hypertrophic gastritis, on the other hand, is thought to mimic peptic ulcer frequently. Nausea, vomiting and gross hemorrhage are considered common in all three types. Similar opinions have been expressed by Carey.¹³ McClure, Sweet-sir and Jankelson, in contrast, concluded that the symptomatology of hypertrophic gastritis and atrophy is similar, except that excessive fatiguability is more common in the latter.⁶

Gordon studied seventy-eight patients with chronic gastritis, all of whom had upper abdominal distress.¹⁴ He correlated symptoms with gastroscopic observations in two groups of patients and found that those with ulcer-like symptoms usually had hypertrophic gastritis whereas those with early graying of the hair, weakness, excessive fatigue, anorexia, vomiting and epigastric distress more often had atrophy of the gastric mucosa. It was not possible to state that the patients in the latter group did not have mild or incipient pernicious anemia. The symptoms of persons with superficial gastritis, who comprised 53 per cent of the entire group, fell into neither category. The author suggested that superficial gastritis and atrophy of the gastric mucosa are usually "incidents in the course of a neurosis, and similar to neurodermatitis in their significance."

Symptoms accompanying hypertrophic gastritis have been likened to those of peptic ulcer by others.¹⁵⁻¹⁹ The symptoms of fifty patients with superficial gastritis were analyzed by Bank and Renshaw.²⁰ Our findings are remarkably similar to theirs, the widest divergence occurring in the incidence of diarrhea: 16 per cent of their patients to 4 per cent of ours. In the studies on dyspeptic soldiers recorded by Halsted *et al.*¹⁰ the symptoms were the same in patients with gastroscopic abnormalities (chiefly superficial gastritis) as in those with normal findings. These symptomatologic data, together with the previously cited observations on alcoholics by Gray,¹² on the healthy volunteers of Fitzgibbon and Long⁷ and

Cutler and Walther⁸ and on the soldiers of Berk,¹¹ are the only analyses found in the literature which include persons with normal gastric mucosae.

Except for the inclusion of patients with normal gastroscopic findings, the present study is similar to one by Horner who recorded the symptoms of three groups of fifty patients each, representing superficial and hypertrophic gastritis and atrophy of the gastric mucosa.²¹ The results are similar in many respects, but in some there is a striking difference, the outstanding example being the incidence of epigastric pain with atrophy: none in Horner's series and 44 per cent in the present group. The occurrence of epigastric distress in the two groups is approximately the same. Epigastric pain was present in twenty-six of forty-one patients with atrophy described by Schindler and Murphy.²

Maimon and Palmer observed the changes in appearance of the gastric mucosa in fourteen patients (ten with gastric ulcer), each of whom was gastroscoped from four to one hundred times over periods of six months to eleven years.²² Normal findings and the three common types of gastritis were found, sometimes in the same patient, but it was "not . . . possible to correlate the appearance of the gastric mucosa with symptoms of any kind." This is in accord with experience previously noted by one of us (W. L. P.).²² Furthermore, the superficial gastritis and the mucosal atrophy following application of moderate doses of roentgen irradiation to the stomach are not accompanied by symptoms.²⁴

X-ray examination may fail to disclose an undetermined but presumably small number of duodenal ulcers in undeformed bulbs; rarely a small, superficial gastric ulcer may escape detection both roentgenographically and gastroscopically. This may account for a small proportion of the ulcer-like symptoms described by our patients, chiefly those with normal gastric mucosae and hypertrophic gastritis, and to a lesser degree those who secrete less acid, the superficial gastritis and gastric mucosal atrophy groups.

Secretion. Faber observed usually a low output of acid in individuals with atrophy of the gastric mucosa.²⁵ Although no evidence was submitted, it was his opinion that chronic inflammation of the stomach produces increased acid secretion. Using the Ewald test, Henning found "hyperacidity" in 11 per cent of patients with "simple" chronic gastritis, normal acidity in 21 per cent, "hypoacidity" in 32 per cent, anacidity in 21 per cent; histamine-anacidity was encountered in 15 per cent.²⁶ In a group of forty-three patients with gastritis Swalm, Jackson and Morrison observed hypo- and anacidity chiefly in those with atrophy.²⁷ Schindler and Murphy found histamine-achlorhydria in nine of thirty-six patients with atrophy of varying degrees.²

Review of three studies²⁸⁻³⁰ on a total of 294 patients with histamine anacidity in the absence of other abnormalities indicated that ninety-nine exhibited atrophy of the gastric mucosa, sixty-six had superficial gastritis, sixty-one had superficial gastritis with atrophy, fifteen demonstrated hypertrophic gastritis, two showed solitary erosions and the mucosae of the remaining fifty-one were normal.

Bank and Renshaw found among fifty patients with superficial gastritis thirteen with histamine-achlorhydria although twenty-five had what was considered to be hyperacidity (more than 50 units of free acid secreted during two hours after an Ewald test meal).²⁰ Only the remaining twelve secreted normal or diminished amounts. These authors suggested the possibility that superficial gastritis, being a precursor of more advanced forms, is sometimes accompanied by stimulation of the acid-secreting cells. When their paper was published in 1939, it was not well known that superficial gastritis is indeed often followed by atrophy.

Gill, in an effort to stimulate acid secretion both centrally and locally, injected insulin and histamine synchronously.³¹ An unstated number of persons with normal mucosae secreted 2.5 to 3.5 cc. per minute while the rate of secretion in persons with

hypertrophic gastritis was 6 to 6.5 cc. of more concentrated acid per minute. Those with gastric mucosal atrophy had anacidity and secreted a volume of less than 1 cc. per minute.

The present findings demonstrate that patients with atrophy of the gastric mucosa produce a low average acid output in response to histamine; the average acid secretion is significantly lower and the incidence of achlorhydria is significantly higher than in persons with other types of gastritis or with normal mucosae. The occurrence of hypersecretion (arbitrarily, more than 600 mg. of free acid during an hour after histamine injection) is less frequent in atrophy than in hypertrophic gastritis or controls.

Diminished acid secretion often occurs in superficial gastritis, as evidenced by the findings of Bank and Renshaw²⁰ as well as our own. The incidence of anacidity, although significantly lower than in atrophy, is significantly higher than in normals or in persons with hypertrophic gastritis. However, that this type of inflammation is compatible with a high output is indicated by secretions of more than 600 mg. of free acid in 12 per cent of our patients and by hyperacidity in one-half of the patients of Bank and Renshaw. Superficial gastritis and subsequent atrophy often occur in individuals in whom a lowered secretion is produced by x-ray therapy directed to the gastric fundus.²⁴

The incidence of histamine anacidity in our patients with hypertrophic gastritis is lower than in the other two types of gastritis. There is a 7.1 per cent probability that the higher incidence of anacidity in hypertrophic gastritis than in normals, as found in this study, is due to chance. This figure, although slightly higher than the usually accepted level of statistical significance, when considered in conjunction with the fact that hypersecretion could also be proved to be more common in this type of gastritis than in the controls, may account for the mean total output of acid being approximately the same in the two groups.

SUMMARY

To evaluate more fully the clinical significance of chronic gastritis in patients with gastrointestinal symptoms, a comparative analysis was made of the symptomatology and of the gastric secretory response to histamine among four groups of patients: fifty patients with atrophy of the gastric mucosa, fifty with superficial gastritis, fifty with hypertrophic gastritis and one hundred individuals in whom the gastric mucosa appeared normal gastroscopically. The absence of other organic disease was established by physical examinations, blood counts, urinalyses, proctoscopies and by x-rays of the gastrointestinal tract. The symptoms, with few exceptions, showed no unequivocal variation among the four groups.

Histamine anacidity was present in 52 per cent of thirty-three patients with atrophy of the gastric mucosa, 27 per cent of twenty-six with superficial gastritis, 14 per cent of twenty-nine with hypertrophic gastritis and 4 per cent of seventy-seven controls. The differences between these incidences and the control value were, with one exception, statistically significant. A quantitative analysis of histamine tests performed in these 165 patients indicated that the smallest average acid secretion was exhibited by patients with atrophy of the gastric mucosa, with superficial gastritis next. A few patients with superficial gastritis, however, secreted large amounts of acid. The average total output of acid in patients with hypertrophic gastritis did not differ significantly from that of individuals with normal mucosae. Nevertheless, a statistically significant proportion of the hypertrophic gastritis group secreted excessive quantities of acid in response to histamine stimulation.

CONCLUSIONS

1. The common types of chronic gastritis apparently produce no symptoms; distress, when present, has no characteristic pattern.
2. Histamine-anacidity occurs most frequently in association with atrophy of the gastric mucosa. The mean secretion of acid

(histamine) is lowest in patients with mucosal atrophy.

3. Some individuals with superficial gastritis are capable of producing large amounts of acid, but the mean histamine secretion is less than it is in persons with hypertrophic gastritis or in controls. The incidence of anacidity in superficial gastritis is second only to that in atrophy.

4. The incidence of histamine anacidity seems greater in patients with hypertrophic gastritis than in persons with normal mucosae, but the mean acid secretion is approximately the same. This may be due to the fact that a certain proportion of individuals with hypertrophic gastritis secrete excessive amounts of acid.

REFERENCES

1. SCHINDLER, R. Gastritis. New York, 1947. Grune & Stratton, Inc.
2. SCHINDLER, R. and MURPHY, H. M. Symptomatology of chronic atrophic gastritis. *Am. J. Digest. Dis.*, 7: 7, 1940.
3. FISHER, R. A. Statistical Methods for Research Workers. 10th ed., p. 97. New York, 1946. G. E. Stechert & Co.
4. SCHINDLER, R. The incidence of various types of gastric disease as revealed by gastroscopic study. *Am. J. M. Sc.*, 197: 509, 1939.
5. CAREY, J. B. Gastroscopic observations in chronic gastritis. *Am. J. Digest. Dis.*, 7: 160, 1940.
6. MCCLURE, C. W., SWEETSIR, F. N. and JANKELSON, I. R. Chronic gastritis: a gastroscopic and clinical study. *New England J. Med.*, 225: 259, 1941.
7. FITZGIBBON, J. H. and LONG, G. B. A gastroscopic study of healthy individuals: a preliminary report, *Gastroenterology*, 1: 67, 1943.
8. CUTLER, J. G. and WALTHER, G. E. The significance of chronic gastritis in an army general hospital, *Gastroenterology*, 5: 112, 1945.
9. RUFFIN, J. M. and BROWN, I. W. The occurrence of gastritis as diagnosed by gastroscopy in gastric neuroses. *Am. J. Digest. Dis.*, 7: 414, 1940.
10. HALSTED, J. A., SCHWARTZ, I. R., ROSEN, S. R., WEINBERG, H. and WYMAN, S. M. Correlated gastroscopic and psychiatric studies of soldiers with chronic non-ulcerative dyspepsia. *Gastroenterology*, 7: 177, 1946.
11. BERK, J. Discussion. *Gastroenterology*, 10: 685, 1948.
12. GRAY, S. Epigastric symptoms in alcoholics with and without gastritis. *Gastroenterology*, 1: 221, 1943.
13. CAREY, J. B. et al. Symposium on symptomatology of chronic gastritis. *Gastroenterology*, 1: 264, 1943.
14. GORDON, W. The symptoms associated with chronic gastritis. *Gastroenterology*, 1: 1013, 1943.
15. COLE, L. G. Hypertrophic gastritis. *M. Clin. North America*, 17: 1, 1933.
16. RIVERS, A. B. and SMITH, L. A. Gastritis simulating peptic ulcer. *Am. J. Digest. Dis.*, 7: 424, 1940.

17. BENEDICT, E. B. Hypertrophic gastritis: gastroscopic and clinical studies. *Gastroenterology*, 1: 62, 1943.
18. GOLD, R. L. Gastroscopic findings in patients with dyspepsia at an army hospital. *Gastroenterology*, 1: 254, 1943.
19. ANNIS, J. W. Gastritis in the military service. *Gastroenterology*, 2: 85, 1944.
20. BANK, J. and RENSHAW, J. F. Chronic superficial gastritis. *J. A. M. A.*, 112: 214, 1939.
21. HORNER, J. L. The symptomatology of chronic gastritis. *Gastroenterology*, 8: 607, 1947.
22. MAIMON, S. N. and PALMER, W. L. Chronic gastritis: observations on its course and significance. *Gastroenterology*, 6, 511, 1946.
23. PALMER, W. L. The stomach and military service. *J. A. M. A.*, 119: 1155, 1942.
24. RICKETTS, W. E., KIRSNER, J. B., HUMPHREYS, E. M. and PALMER, W. L. The effect of irradiation on the gastric mucosa: a gastroscopic and pathologic study. *Gastroenterology*. To be published.
25. FABER, K. Gastritis and Its Consequences. London 1935. Oxford University Press.
26. HENNING, N. Die Entzündung des Magens. Leipzig. 1934. Johann Ambrosius Barth.
27. SWALM, W. A., JACKSON, C. L. and MORRISON, I. Correlation of clinical and gastroscopic findings in chronic gastritis. *Rev. Gastroenterol.*, 3: 219, 1936.
28. SCHINDLER, R., NUTTER, P. B., GROOM, H. E. and PALMER, W. L. Anatomic foundation of anacidity: a gastroscopic study. *Arch. Int. Med.*, 66: 1060, 1940.
29. CAREY, J. B., WETHERBY, M. and YLVIKAKER, R. S. Gastric observations in achlorhydria. *Am. J. Digest. Dis.*, 8: 401, 1941.
30. CHRISTIANSEN, T. Der gastroscopische Befund bei Anäcidität, mit besonderem Hinblick auf den Zusammenhang zwischen den klinischen Symptomen und dem Zustande der Schleimhaut. *Gastroenterologia*, 67: 125, 1942.
31. GILL, M. Discussion on gastritis. *Proc. Roy. Soc. Med.*, 38: 86, 1944.

A Unified Concept of Cardiac Failure*

J. MAXWELL LITTLE, Ph.D.
Winston-Salem, North Carolina

INCREASED venous and atrial pressure observed in cardiac failure has been attributed by various investigators to: (1) a damming of blood, or back pressure, (2) an increase in the blood volume or (3) a decrease in the capacity of the venous side of the circulatory system.

As a result of work with the heart-lung preparation Starling proposed that the increase in venous pressure seen in cardiac failure is due to a "back-pressure" or "damming" phenomenon. This concept has been discussed at length by Harrison.¹ Starr² observed that in patients dying of cardiac failure the venous pressure was elevated after death. He believed that the increased venous pressure during life could not be ascribed to a damming of the blood and therefore he questioned the validity of this concept. Warren and Stead³ observed an increase in body weight and in plasma volume in patients with congestive failure before there was an appreciable increase in venous pressure, and they ascribed the increase in venous pressure to an increased blood volume due to retention of salt and water. Merrill⁴ has reported salt retention in congestive failure due to a decreased glomerular filtration rate.

If it be accepted that the increased venous pressure seen in congestive failure is due to an increased blood volume, or if it be accepted that it is due to damming of the blood, then one must turn to other explanations for the increased venous pressure seen in cardiac failure due to anemia since McMichael⁶ has called attention to the report of Sharpey-Schafer that in anemic heart failure with an increased cardiac out-

put the blood volume is often low in the presence of considerable increases in venous pressure. McMichael states: "In these cases of 'anemic heart failure' the rise in venous pressure cannot be ascribed to failure of the heart to keep on pumping blood through the body at an adequate rate, as the output is usually more than double the normal value. The pulse pressure is increased, indicating that the arterioles are dilated (the output being high and the mean arterial pressure somewhat reduced). Since the volume of blood in circulation (often below 3 liters) must be equal to the capacity of the total vascular bed, the latter must be markedly reduced. This reduction does not take place on the arterial side; as the larger veins are full and often distended, it must take place in the capillaries and venules. It is on such clinical evidence that we find it necessary to postulate an active venomotor mechanism for maintaining and even raising the venous pressure to the required level."

UNIFIED CONCEPT OF CARDIAC FAILURE

At the present time there is no single unified concept of cardiac failure which will explain the increase in atrial pressure seen in all types of cardiac failure. Evidence is presented in this paper which supports the view that the increase in blood volume will not account adequately for the increase in atrial pressure seen in congestive heart failure. Evidence is also presented which supports the hypothesis that a decrease in the mixed venous pO_2 (partial pressure of oxygen) probably serves as a stimulus which results in an increased cardiac output and a decreased venous capacity in the normal

* From The Department of Physiology and Pharmacology, The Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.

individual, the decreased venous capacity being due to venoconstriction. The mechanism for these effects may be by means of reflexes or by means of humoral control, or both. Normally with an increased oxygen demand, such as in exercise, there would be

tistical analysis.⁷ In some instances new data have been derived by calculation from published observations.

Relationship between Blood Volume and Atrial or Venous Pressure. If the increased venous pressure in congestive failure were due to an

TABLE I
CORRELATION BETWEEN VENOUS PRESSURE AND BLOOD VOLUME IN CONGESTIVE HEART FAILURE

Comparison	Refer- ence	No. of Pairs of Observa- tions	Mean		r	t	P (%)
			Venous Pressure (mm. H ₂ O)	Blood Vol. (cc.)			
Venous pressure versus blood volume	(8)	19	205	6083	0.149	0.620	> 50
Venous pressure versus blood volume	(9)	21	168	6183	0.379	1.698	> 5
Venous pressure versus excess blood volume ^x	(9)	20	171	1617 _x	0.529	2.687	< 5
Maximum decrease in venous pressure versus cor- responding decrease in blood volume ^{xx}	(9)	15	106 _{xx}	1217	0.093	0.314	> 50

x—excess blood volume = determined blood volume—predicted blood volume.
xx—maximum decrease in venous pressure with treatment = maximum venous pressure—lowest venous pressure. The difference in the values for the determined corresponding blood volumes was used for comparison.
r = correlation coefficient.
t = “Students” t value for significance.
P = The probability of chance occurrence of the correlation.

only a slight or moderate rise in the central venous or atrial pressure, depending upon the adequacy of the increased cardiac output in response to the decreased mixed venous pO₂. Theoretically if the cardiac response were entirely adequate, there would be no increase in central venous pressure in spite of the decreased venous capacity.

In cardiac failure, whether it be acute failure, low output failure or high output failure, the cardiac response to the decreased mixed venous pO₂ would be inadequate due either to disease or to a relatively excessive oxygen demand, or to a combination of the two; and the venoconstriction resulting from the decreased mixed venous pO₂ would cause a considerable increase in central venous or atrial pressure.

ANALYSIS OF PRESENT CONCEPTS

The data presented herein were taken from the literature and subjected to sta-

increased blood volume, there should be a good statistical correlation between these two sets of data in the same patient. In Table I the correlation coefficient between the venous pressure and the blood volume in congestive failure has been calculated as well as the probability of chance occurrence of this correlation. It will be seen that there is no significant correlation between venous pressure and blood volume in these patients. Gibson and Evans⁹ estimated the excess blood volume in their patients and a significant correlation between the estimated excess blood volume and the venous pressure was found. With treatment these patients showed a decrease in venous pressure and blood volume. However, the correlation between the maximum decrease in venous pressure and the corresponding blood volume change was found to be insignificant.

The relation between venous pressure and per cent deviation from the predicted

normal blood volume while under treatment in five of Gibson's and Evans' patients will be found in Figure 1. It will be seen that at first there was considerable decrease in venous pressure which was accompanied by little or no decrease in the excess blood volume. Later there was a slight decrease in venous pressure accompanied by a considerable decrease in the excess blood volume. It will be seen also that in the patients illustrated the venous pressure value at the beginning of treatment was not related to the percentage of blood volume in excess of the estimated normal.

Although these data do not exclude the possibility that an excess blood volume contributes to the elevation of venous pressure in congestive heart failure, they do indicate that there is some other factor or factors concerned in the elevation of venous pressure in this condition. In anemic heart failure the elevation of venous pressure cannot be ascribed to an excess blood volume for the blood volume is usually either normal or diminished in this condition.⁶

Relationship between Cardiac Index and Atrial or Central Venous Pressure. In Table II it will be seen that in two groups of patients with congestive heart failure there were significant negative correlation and regression coefficients when the cardiac index and atrial or central venous pressures were compared. Of course, a significant correlation *per se* gives no information regarding causative factors in a relationship. These data could be interpreted (1) as meaning that an elevation of atrial or venous pressure causes a decreased cardiac output, (2) that a decreased cardiac index causes an elevated venous pressure in congestive failure or (3) that a decreased cardiac index affects some other function or mechanism which in turn is responsible for the elevation of venous pressure in congestive heart failure.

Considering the first possibility this interpretation of the data would fit the widely accepted concept of the operation of Star-

ling's law in congestive failure.⁶ However, this interpretation contributes no information as to the cause of the elevated venous pressure in congestive heart failure.

Considering the second possibility one might say that this interpretation favors the damming or back-pressure theory of the elevation of venous pressure in congestive

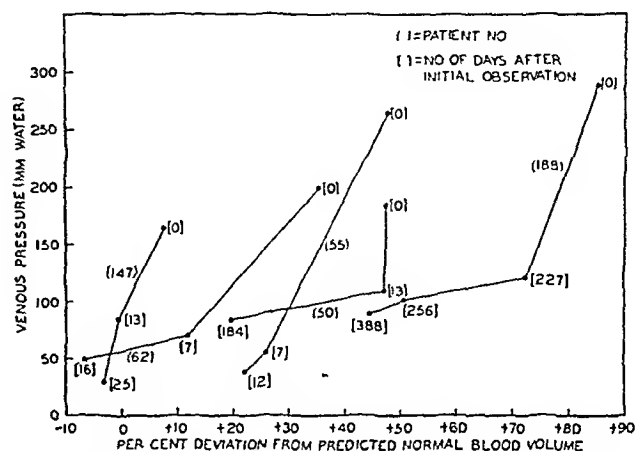


FIG. 1. Relationship between venous pressure and the excess blood volume during treatment in patients with congestive heart failure. Data taken from Gibson and Evans.⁹

failure. However, it has been shown^{5,15} that when the "competency" of the dog's heart was decreased there was no significant increase in the resting venous pressure. Therefore, there may be considerable doubt that the damming or back-pressure theory of the elevation of venous pressure in congestive failure is true. Of course, this theory cannot explain the elevated venous pressure seen in anemic heart failure for the cardiac index is increased in this condition.

Considering the third possibility this is the interpretation proposed by those who favor elevation in blood volume as the causative factor in elevation in venous pressure in congestive failure.^{3,4} However, a decrease in cardiac index would probably mean that the supply to the tissues of various substances, including oxygen, would be diminished and this may cause an alteration in some mechanism, other than a change in blood volume, which would affect the venous pressure.

FURTHER RELATIONSHIPS IN CARDIAC FAILURE

Relationship between Oxygen Supply to the Tissues and Oxygen Consumption in Normal Subjects and in Patients with Cardiac or Respiratory Disease. As an expression of the adequacy with which the heart meets the tissue demands for oxygen the ratio of oxygen supply to the tissues per square

in Table III. It will be seen that significant differences between mean values for O.I. occur in the following: normal at rest and congestive failure at rest, normal with exercise and congestive failure with exercise, normal with exercise and mitral stenosis with exercise, normal at rest and normal with exercise and congestive failure

TABLE II
CORRELATION AND REGRESSION COEFFICIENTS FOR VARIOUS MEASUREMENTS IN PATIENTS
WITH CONGESTIVE HEART FAILURE

A	V.P. on C.I.	A.P. on C.I.	A.P. on C.I.	A-VO ₂ on C.I.	A.P. on AO ₂	A.P. on VO ₂	A.P. on A-VO ₂	A.P. on A-VO ₂	V.P. on A-VO ₂	A.P. on ApO ₂	A.P. on VpO ₂
B											
Reference.	(4)	(4)	(10)	(4)	(10)	(10)	(10)	(4)	(4)	(10)	(10)
Pairs of observations	13	19	47	32	47	47	47	19	12	14	14
Mean for A.	140	142	146	6.5	146	146	146	142	144	158	158
σ for A	65.72	65.15	91.87	1.66	91.87	91.87	91.87	65.15	67.18	103.57	103.57
Mean for B	2.4	2.6	2.1	2.5	15.4	8.0	7.3	6.8	6.0	55.8	21.8
σ for B	0.68	0.84	0.50	0.77	2.10	2.43	1.58	1.53	1.74	12.27	5.60
Correlation coefficient (r)	-0.69	-0.46	-0.47	-0.58	-0.14	-0.37	+0.47	+0.65	+0.73	+0.04	-0.56
t for r	3.105	2.110	3.525	3.820	0.955	2.616	3.525	3.510	3.358	0.139	2.341
P for r (%)	< 1	< 5	< 1	< 1	> 5	< 5	< 1	< 1	< 1	> 50	< 5
Regression coefficient (R.C.)	-65.57	-37.31	-89.635	-1.357	-6.309	-16.70	+29.195	+27.72	+28.31	+0.403	-10.358
t for R.C.	3.224	2.192	3.751	4.406	0.976	3.332	3.760	3.536	3.418	0.166	2.320
P for R.C. (%)	< 1	< 5	< 1	< 1	> 5	< 1	< 1	< 1	< 1	> 50	< 5

V.P. = venous pressure in mm. water or saline.

A.P. = arterial pressure in mm. water or saline.

C.I. = cardiac index (cardiac output in l./min./sq. M.).

A-VO₂ = arterial-venous O₂ difference in cc./100 cc.

AO₂ = arterial O₂ content in cc./100 cc.

VO₂ = mixed venous O₂ content in cc./100 cc.

ApO₂ = arterial O₂ tension in mm. Hg

VpO₂ = mixed venous O₂ tension in mm. Hg.

σ = standard deviation of the mean.

t = "Students" t value for significance

P = Probability of chance occurrence

meter of body surface to the oxygen consumption per square meter has been calculated. In this oxygen index, O.I. = $\frac{\text{O}_2 \text{ supply/sq. M.}}{\text{O}_2 \text{ consumption/sq. M.}}$

the oxygen supply was calculated from the cardiac index in l./min. and the arterial oxygen content in cc./l.* The oxygen consumption was reported^{10,13,14} and these data are presented

* Since the cardiac output occurs in both the numerator and denominator, an equivalent mathematical expression of this relationship is:

$$\text{O.I.} = \frac{\text{arterial O}_2 \text{ content in vol. } \%}{\text{A-V O}_2 \text{ difference in vol. } \%}$$

at rest and congestive failure with exercise. Non-significant differences between mean values of O.I. occurred in: normal at rest and mitral stenosis at rest, normal at rest and pulmonary emphysema at rest and normal with exercise and pulmonary emphysema with exercise.

It has been shown that in the normal subject with exercise the O.I. is significantly lower than at rest. This is interpreted as meaning that in the normal subject, with the degree of exercise used in these experiments, the heart is unable to maintain the normal O.I. and therefore the A-V oxygen

difference must increase; the mixed venous oxygen content and the mixed venous pO_2 must decrease below the normal resting value. In the blood leaving the tissues there is a relative hypoxia. The O.I. in congestive failure at rest or with exercise is significantly lower than the corresponding values in the normal subject. This means that in congestive failure, even at rest, there is a failure of the heart to supply the normal amount of oxygen to the tissues. In the patients with mitral stenosis the difference from the normal O.I. at rest is not significant while with exercise it is significant, and the O.I. is only slightly greater than in the patients with congestive failure during exercise. This indicates that in the patients with mitral stenosis it is only during exercise that a failure of oxygen supply to the tissues occurs. In patients with pulmonary emphysema there was no failure of the heart to supply the normal amount of oxygen to the tissues with or without exercise. This is shown by the fact that the O.I. was not significantly different from values in the normal subjects under the same circumstances. In four cases¹⁰ of high output failure at rest, anemia and hyperthyroidism the mean value for O.I. was 2.49 which is only slightly greater than the value in congestive failure at rest. This means that in high output failure there is a failure of the heart to supply oxygen to the tissues.

It is seen then that the common feature of congestive failure, mitral stenosis with exercise and high output cardiac failure is failure of the heart to supply oxygen to the tissues in sufficient amounts. This means that there would be a considerable hypoxia of the blood leaving the tissues under these circumstances.

Some idea of the critical value of the O.I. which is indicative of cardiac failure may be derived by subtracting 2σ from the mean normal value¹⁴ and adding 2σ to the mean value for patients with congestive failure at rest.¹⁰ (Table III.) It will be seen that the overlapping critical range is 3.18 to 3.53.

Relationship between Atrial or Central Venous Pressure and Arterial and Mixed Venous Oxygen Content, Arteriovenous Oxygen Difference and Arterial and Mixed Venous pO_2 . In Table II it will be seen that there are significant negative correlation and regression coefficients between the atrial pressure and mixed venous oxygen content and mixed venous oxygen tension (pO_2).^{*} There are significant positive correlation and regression coefficients between the atrial or venous pressure and A-V O_2 difference. The correlation and regression coefficients between the atrial pressure and the arterial oxygen content or arterial oxygen partial pressure (pO_2) were not significant.

Again these correlations give no information within themselves as to causative factors. However, if an elevation in venous pressure were causing the oxygen changes noted, one would expect to find an increase in the A-V oxygen difference whenever an elevation of venous pressure occurred. Sharpey-Schafer¹⁶ reported that in uncomplicated chronic anemia, with a normal venous pressure and a mean cardiac output of 7.6 l/min., the mean A-V oxygen difference was 3.4 cc./100 cc.; while in anemic heart failure, with an elevated venous pressure and a mean cardiac output of 9.4 l/min., the mean A-V oxygen difference was 3.1 cc./100 cc. The elevation in venous pressure was not accompanied by an increase in the A-V oxygen difference.

If the oxygen changes noted are responsible for the elevation in atrial and venous pressure in congestive heart failure, which of these changes might be the causative factor? It should be remembered that the mixed venous O_2 is not directly related to the mixed venous oxygen content since it is dependent upon the per cent saturation of the mixed venous blood with oxygen.

Certain comparisons between normal subjects and patients with uncomplicated anemia give some information regarding the causative factor. Cournand et al.¹²

^{*} The pO_2 was calculated from the per cent arterial saturation, the arterial O_2 content and the mixed venous oxygen content using the oxygen dissociation curve at a pH of 7.44.

reported the following mean values in fifteen normal subjects: atrial pressure, 33 mm. water; A-V oxygen difference, 4.5 vol. per cent; mixed venous pO_2 , 34 mm. Hg (calculated from the oxygen saturation of

vol. per cent; calculated* mixed venous pO_2 , 30.7 mm. Hg and mixed venous oxygen content, 5.3 vol. per cent. In the patients with uncomplicated chronic anemia the only measurements with which we are

TABLE III
COMPARISON OF OXYGEN INDEX VALUES IN NORMAL SUBJECTS AND SUBJECTS WITH DISEASE

Type of Subject	Refer- ence	No. of Sub- jects	Mean Value O.I.	σ for Mean of O.I.	Difference between Mean Values	<i>t</i> for Difference	Probability of Chance Occurrence of Difference (%)
Normal at rest. . .	(14)	20	4.79	0.805	2.55	14.119	< 1
Congestive failure at rest	(10)	48	2.24	0.644			
Normal at rest. . .	(13)	8	4.50	0.957	1.76	4.889	< 1
Congestive failure at rest.	(13)	9	2.74	0.476			
Normal at rest . .	(13)	8	4.50		0.92	2.120	> 5
Mitral stenosis at rest	(13)	7	3.58	0.673			
Normal at rest.	(13)	8	4.50		0.64	1.293	> 5
Pulmonary emphysema at rest	(13)	5	3.86	0.688			
Normal with exercise .	(13)	8	3.30	0.883	1.30	4.047	< 1
Congestive failure with exercise	(13)	9	2.00	0.376			
Normal with exercise	(13)	8	3.30		0.94	2.271	< 5
Mitral stenosis with exercise	(13)	7	2.36	0.689			
Normal with exercise.	(13)	8	3.30		0.39	0.911	> 5
Pulmonary emphysema with exercise	(13)	5	2.91	0.430			
Normal at rest.	(13)	8	4.50		1.20	2.609	< 5
Normal with exercise .	(13)	8	3.30				
Congestive failure at rest	(13)	9	2.74		0.74	3.663	< 1
Congestive failure with exercise.	(13)	9	2.00				

$$O.I. = \frac{\text{oxygen supply/sq. M.}}{\text{oxygen consumption/sq. M.}}$$

σ = standard deviation.

t = "Students" *t* value for significance.

mixed venous blood using the oxygen dissociation curve at pH 7.44). A value for the mixed venous oxygen content was not given but it may be calculated to be 12.1 vol. per cent since the mean arterial oxygen content was 16.6 vol. per cent and the mean A-V oxygen difference was 4.5 vol. per cent. Compare with these data the report of Brannon et al.¹¹ in patients with uncomplicated chronic anemia: atrial pressure, 41 mm. water; A-V oxygen difference, 3.1

concerned which were normal were the atrial pressure and the mixed venous pO_2 .

Of the three oxygen factors considered the evidence is suggestive that a decreased mixed venous pO_2 is related in a causative manner to the elevation of atrial or venous

* Only those patients were used in whom there was good agreement between the arterial O_2 content as determined and as calculated from the hemoglobin content. It was assumed that the arterial O_2 saturation was 95 per cent and the oxygen dissociation curve at pH 7.44 was used.

pressure since marked alterations in the A-V oxygen difference and mixed venous oxygen content were not associated with an elevated atrial pressure.

HYPOTHESIS

It has been shown that: (1) the increased blood volume does not adequately explain the elevated venous pressure in congestive heart failure, and an increased blood volume cannot explain the elevated venous pressure in anemic heart failure; (2) although the cardiac index is related inversely to the venous pressure in congestive heart failure, there is a reasonable doubt that this can be explained on the basis of damming or back-pressure, and this mechanism cannot explain the elevated venous pressure in anemic heart failure; (3) there is a definite relationship between cardiac failure, congestive and anemic, and the ratio of the tissue oxygen supply and tissue oxygen consumption; (4) there are significant correlations between the atrial or venous pressure in congestive heart failure and the A-V oxygen difference, the mixed venous oxygen content and the mixed venous pO_2 and (5) the evidence favors a causative relationship between the mixed venous pO_2 and the atrial or venous pressure.

On the basis of this information it is postulated that normally when there is a decreased mixed venous pO_2 in response to increased oxygen utilization or inadequate blood oxygen capacity, the cardiac output increases and the venous capacity decreases. These functions may be controlled by the same or different reflex or humoral mechanisms but they have a common stimulus—decreased mixed venous pO_2 . The decreased venous capacity would permit an increased cardiac output without a marked decrease in atrial and ventricular filling pressures. The net effect of these mechanisms on the atrial pressure will depend upon the adequacy of response of the heart to the stimulus. If the response of the heart is inadequate, as in acute, congestive or anemic heart failure,[†] the net effect on venous or atrial pressure would be a marked increase.

During exercise in the normal subject again the degree of elevation of venous or atrial pressure would be dependent upon the response of the heart. In cardiac failure the net effect of exercise would be a marked increase in venous or atrial pressure since the cardiac response is inadequate while venoconstriction would be unimpaired. In individuals in whom the resting oxygen supply to the tissues was markedly decreased, as in marked cardiac failure or anemia if of a sufficient degree, the net effect on venous or atrial pressure would be a marked elevation.

The concept just postulated does not imply that a decrease in mixed venous pO_2 , *per se*, with consequent venoconstriction as in failure of oxygenation would necessarily result in an elevation of venous or atrial pressure. It would depend upon both the decrease in venous capacity and the capacity of the heart to increase its output.

In support of this concept are the experiments of Landis et al.⁵ They found that exercise in normal anesthetized dogs reduced venous pressure. If the heart were embarrassed by coronary artery ligation or atrial fibrillation, there was no elevation of venous pressure at rest. However, if these dogs were exercised, there was an elevation of atrial pressure. A diminution in cardiac competency alone left the venous pressure unaffected but in the presence of increased oxygen utilization (exercise) elevated venous pressure resulted. Starr et al.¹⁵ also have reported that in asphyxia there is an increase in the arterial and venous pressures as well as in the vigor of cardiac contraction. In discussing these experiments they say: "Such a generalized increase in intravascular pressure cannot be explained as a mechanical consequence of changes in cardiac activity and arteriolar resistance. Occurring far too rapidly to allow the assumption of an increase in blood volume with passive distention of vessels, a widespread increase in vascular tone, without compensatory relaxation elsewhere is the explanation which naturally suggests itself." Of course, an outstanding feature of

asphyxia would be a decreased mixed venous pO_2 .

Other evidence in support of this concept may be derived from studies of venous pressure during exercise in normal subjects.¹⁷ These authors report that with moderate exercise the venous pressure increases to a maximum which is maintained throughout the exercise but with heavy exercise the venous pressure increases steadily until fatigue ensues. There was a roughly linear relationship between venous pressure and work load. After exercise the venous pressure ordinarily returned to normal within a few minutes. However, after heavy work the time required for a return to the control value was often twenty-two to twenty-seven minutes. These data support the concept that venous pressure is related to the oxygen debt and, therefore, to the mixed venous pO_2 .

Results obtained in man during acute anoxia by Motley et al.¹⁸ appear to refute the concept presented herein. In five subjects breathing 10 per cent oxygen for fifteen to twenty minutes it was found at the end of this time that there was an 8.8 per cent decrease in cardiac output and a 67 per cent increase in diastolic right ventricular pressure; a slight rise in systolic arterial pressure with no appreciable change in diastolic or mean arterial pressures was also found. The average increase in cardiac rate was from a control of 67 to a rate of 80. We have calculated the mixed venous pO_2 to be approximately 24 mm Hg. The increase in diastolic right ventricular pressure may be due to an increase in mean pulmonary arterial pressure, which was found, and the slight decrease in cardiac output may have been due to a decrease in left atrial pressure. However, it is very difficult to analyze these findings with relation to the concept presented here for the arterial hypoxia certainly results in cardiovascular reflexes which may modify any effects usually produced by mixed venous hypoxia. In addition the degree of hypoxia attained in these experiments at least approaches the

previously reported critical level¹⁹ and there are no data showing progressive changes.

It is quite probable that an increase in blood volume will contribute to an elevation of atrial and venous pressure. However, the concept presented herein will explain the events seen in cardiac failure regardless of the type and etiology. The nature of the postulated reflexes or humoral mechanisms is unknown but the situation is quite analogous to that found on the arterial side—mediation of cardiac and vascular reflexes through stimulation of the chemoreceptors in the carotid body and the aortic arch.

Acknowledgments. The author is indebted to Dr. George Givens and Mr. Latham Peak for some of the statistical analyses.

REFERENCES

1. HARRISON, T. R. Failure of the Circulation. Baltimore, 1939. The Williams & Wilkins Co.
2. STARR, I. Role of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. II. Clinical and experimental studies. *Am. J. M. Sc.*, 199: 40, 1940.
3. WARREN, J. V. and STEAD, E. A., JR. Fluid dynamics in chronic congestive heart failure. An interpretation of the mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure. *Arch. Int. Med.*, 73: 138, 1944.
4. MERRILL, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema. *J. Clin. Investigation*, 25: 389, 1946.
5. LANDIS, E. M., BROWN, E., FAUTEUX, M. and WIST, C. Central venous pressure in relation to cardiac "competence," blood volume and exercise. *J. Clin. Investigation*, 25: 237, 1946.
6. McMICHAEAL, J. Circulatory failure studied by means of venous catheterization. *Adv. Int. Med.*, 2: 64, 1947.
7. SNEDECOR, G. W. Statistical Methods. Ames, Ia., 1940. The Iowa State College Press.
8. MOKOTOFF, R., ROSS, G. and LEITER, L. Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. *J. Clin. Investigation*, 27: 1, 1948.
9. GIBSON, J. G. and EVANS, W. A., JR. Clinical studies of blood volume, venous pressure and blood velocity rate in chronic congestive heart failure. *J. Clin. Investigation*, 16: 851, 1937.
10. STEAD, E. A., JR., WARREN, J. V. and BRANNON, E. S. Cardiac output in congestive heart failure. *Am. Heart J.*, 35: 529, 1948.

11. BRANNON, E. S., MERRILL, A. J., WARREN, J. V. and STEAD, E. A., JR. The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. *J. Clin. Investigation*, 24: 332, 1945.
12. Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lauson, H. D., Gregersen, M. I. and Richards, D. W., JR. Studies of the circulation in clinical shock. *Surgery*, 13: 964, 1943.
13. Hickam, J. B. and Cargill, W. H. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J. Clin. Investigation*, 27: 10, 1948.
14. Stead, E. A., JR., Warren, J. V., Merrill, A. J. and Brannon, E. S. The cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting. *J. Clin. Investigation*, 24: 326, 1945.
15. Starr, I., Jeffers, W. A. and Meade, R. H., JR. The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease. *Am. Heart J.*, 26: 291, 1943.
16. Sharpey-Schafer, E. P. Cardiac output in severe anemia. *Clin. Sc.*, 5: 125, 1944.
17. Schneider, E. C. and Collins, R. Venous pressure responses to exercise. *Am. J. Physiol.*, 121: 574, 1938.
18. Motley, H. L., Cournand, A., Werko, L., Himmelstein, A. and Dresdale, D. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Am. J. Physiol.*, 150: 315, 1947.
19. Van Liere, E. J. Anoxia, Its Effect on the Body. Chicago, 1942. The University of Chicago Press.

Seminars on Antibiotics

Dosage Forms of Penicillin for Systemic Infections*

CHESTER S. KEEFER, M.D.

Boston, Massachusetts

PENICILLIN continues to be the most widely used antibiotic agent in medical practice today. The three advances that have been made in the recent past have been the development of new dosage forms and of new salts of penicillin and a more precise definition of the indications for oral therapy. In addition further advances have been made in dosage schedules. This communication is an attempt to sum up some of the current views concerning penicillin treatment with different dosage forms.

DOSAGE FORMS FOR PARENTERAL ADMINISTRATION OF PENICILLIN

The most common dosage forms for parenteral administration are (1) sodium or potassium salts of penicillin G for injection in aqueous solution; (2) procaine penicillin G suspended in oil, water or oil and aluminum monostearate; (3) combinations of crystalline sodium or potassium and procaine penicillin for dispensing in an aqueous medium.

From the beginning of penicillin therapy the water-soluble salts have been widely used. These have been injected continuously by the intravenous or intramuscular method or, more commonly, intermittently by the intramuscular route. When the intermittent injections are used, an attempt is made by many to inject a sufficient amount at regular intervals so that penicillin is present in the blood and tissues at all times during the twenty-four-hour period. This form of treatment has been designated *continuous* peni-

cillin therapy. When penicillin is given intermittently but the injections are spaced in such a way that penicillin is not detected in the blood and tissue at all times during the twenty-four-hour period, it has been called *discontinuous* therapy. It has been recognized since the beginning of the use of penicillin that it was unnecessary to maintain a concentration of penicillin in the blood and tissues throughout the day in order to obtain optimum therapeutic results. Every infection varies in its susceptibility to penicillin so that it is not surprising that a wide variety of dosage schedules have proved to be effective. In general it can be said that the goal of treatment should be to effect recovery from infection in the shortest period of time with the least amount of inconvenience to the patient. It is for these reasons that every infection presents an individual problem.

When the aqueous soluble salts of penicillin are used in the treatment of infection, the first question to be decided is how much is to be injected in the twenty-four-hour period and how frequently should the injections be made. Inasmuch as the *minimum effective dose* has never been established for all infections it is impossible to make any precise statements about every susceptible infection. It can be said, however, that in the treatment of common infections such as pneumococcal pneumonia, hemolytic streptococcal infections and gonococcal infections the general trend in treatment with aqueous soluble salts has been to increase the amount of penicillin that is injected at each injection.

* From the Boston University School of Medicine, the Evans Memorial and the Massachusetts Memorial Hospital, Boston, Mass.

and to increase the interval between injections. For example, in the treatment of lobar pneumonia it has been found that the injection of 200,000 or 300,000 units twice daily is as effective as injecting 25,000 units every three or four hours. Thus the trend has been toward discontinuous therapy when the aqueous salts of penicillin are employed in treatment. When discontinuous treatment with aqueous preparations is used, the concentration of penicillin in the plasma and in the tissues is optimal during the first hours after injection and then declines rapidly over a period of four to six hours. When sodium or potassium penicillin G in aqueous solution is used for the treatment of infections by the discontinuous method, a decision must be made as to how much is needed during the twenty-four-hour period and how often it is to be injected. This decision will depend upon the type of infection that is being treated and the patient's response to therapy.

INDICATIONS FOR USE OF CRYSTALLINE PENICILLIN G

Crystalline penicillin G must be used for all oral therapy. It is also required in preparation of all solutions for topical application, such as intrathecal, intrapleural, intra-abdominal, intra-articular, intratracheal and in preparation of aerosol solutions.

Crystalline penicillin G should also be used parenterally in combination with procaine penicillin G in serious infections so that high plasma concentrations of penicillin may be obtained promptly. These so-called "booster" doses of penicillin may be repeated twice daily when the organisms are relatively resistant or when the infection is located in an area of the body where penicillin diffuses with difficulty.

PROCAINE PENICILLIN G

In order that the total number of injections of penicillin might be reduced to a minimum, procaine penicillin G, a salt of penicillin that is relatively insoluble in

water, was developed. This salt can be suspended in sesame oil or in water. When water is used for the suspending agent, a small amount of detergent is added to the penicillin so that it may be suspended evenly. When 300,000 units of procaine penicillin are suspended in 1 ml. of oil or water and injected into the muscles, the penicillin is slowly released from the deposit. The maximum plasma concentration of penicillin is reached within one to two hours. After this period of time the plasma concentration decreases slowly so that in practically all patients the plasma concentration will be above 0.05 units per ml. at the end of twelve hours and in at least 80 per cent of the patients for twenty-four hours. The differences between plasma concentration of penicillin when procaine penicillin or crystalline penicillin is injected are as follows: Maximum plasma concentrations following aqueous sodium penicillin G are observed within ten to fifteen minutes after injection; they are always greater than is observed following the injection of a similar amount of procaine penicillin G, but penicillin disappears from the circulating blood at a much more rapid rate. The plasma concentration of penicillin following the injection of 300,000 units of aqueous penicillin is usually about the same at the end of one hour as that which is observed at the end of twelve hours following the same dose of procaine penicillin.

In an attempt to produce an initially high plasma concentration of penicillin during the first thirty minutes to an hour crystalline sodium or potassium penicillin G has been combined with procaine penicillin G so that in 1 ml. of the aqueous material 100,000 units of the crystalline soluble salt is combined with 300,000 units of the procaine salt.

When procaine penicillin G is suspended in oil and aluminum monostearate is added, the penicillin is absorbed more slowly and more uniformly. The initial and peak plasma concentrations of penicillin are lower than when other preparations are used but plasma concentrations of 0.05

are present for a longer period of time. For example, following the intramuscular injection of 300,000 units of procaine penicillin G in oil and aluminum monostearate, the plasma concentration at the end of one hour will average 0.25 units; when this is compared with the concentration at the end of one hour following the injection of the same salt without aluminum stearate, it is found to be about one-sixth as great (average 1.5 units). The plasma concentration of penicillin usually does not decrease below 0.05 for at least ninety-six hours in most cases and this concentration is frequently maintained for as long as one hundred twenty hours. When doses of 600,000 units are injected, a relatively constant plasma concentration is maintained at a higher level over a period of four or five days but the initial plasma concentrations are not commensurately greater. All of the studies with this preparation show that it is exceedingly difficult to obtain a high plasma concentration but that the level obtained can be greatly prolonged. These observations show that procaine penicillin G with aluminum monostearate is released from tissues very slowly indeed when compared with other preparations. It can be said that following the injection of 300,000 units of procaine penicillin G in water or oil this amount is available to the tissues for a twenty-four-hour period and in a concentration that is usually considered to be adequate for controlling the vast majority of penicillin-sensitive infections. Following the injection of 300,000 units of the same salt combined with aluminum stearate, this amount of penicillin is available to the tissues over a period of ninety-six hours but the concentration of penicillin is always lower during the first twenty-four hours of treatment than when no aluminum monostearate is used.

Indications and Dosage. It is now established that a single daily injection of procaine penicillin G in oil or water is adequate for the effective treatment of most infections requiring penicillin. Larger doses, i.e., 600,000 units once or twice daily should be given in infections caused by organisms that

are only moderately sensitive to penicillin, i.e., staphylococcal infections and *Streptococcus viridans*.

When procaine penicillin G in oil and aluminum monostearate is employed the injections may be spaced several days apart. This is desirable in ambulatory patients or in mild infections when it is unnecessary to see patients every day. According to the experience of Stollerman, Roston and Toharsky,⁴ infections due to bacteria with a resistance of 0.1 unit or less may be treated with one injection of 3.0 million units since a plasma concentration of 0.1 units per ml. can be maintained for a week following such a dose. At the time their paper was published they were recommending a single intramuscular injection of procaine penicillin G with or without aluminum monostearate daily. In our own experience with hospitalized patients we have used one injection a day of procaine penicillin G in oil or water for the treatment of all moderately severe infections.

The dosage schedules of procaine penicillin G that we have used with success have been as follows: *Pneumococcus pneumoniae*, 300,000 units once daily for five to seven days; gonorrhea, 300,000 units, one injection; subacute bacterial endocarditis, 300,000 to 600,000 units once or twice daily for six to eight weeks; streptococcal infections of the throat, 300,000 units once daily for five to seven days; staphylococcal infections, 300,000 to 600,000 units once or twice daily for seven to fourteen days; prophylactic use, 300,000 units once daily; postoperatively, 300,000 units daily; tooth extractions, 300,000 units once, one hour before extraction; puerperium, 300,000 units daily for five days; tonsillectomy, 300,000 units once.

ORAL PENICILLIN

Penicillin is available for oral administration in the form of either the sodium or potassium salts of crystalline penicillin. Some preparations are combined with a buffer for the purpose of increasing the stability of the product and also for its acid-

neutralizing capacity when introduced into the stomach. It has been demonstrated repeatedly that it is not necessary to use a buffered preparation in order to obtain a satisfactory therapeutic result.

More and more patients who require penicillin are receiving it by mouth. This is a logical way to give any potent drug provided it is absorbed from the gastrointestinal tract. It is convenient, it decreases nursing care and discomfort for the patient, it saves the time of the physician and nurse and it should cost the patient no more. What is of more importance is the fact that it has been demonstrated repeatedly that the oral route is as effective as the parenteral route when adequate doses of penicillin are used. The therapeutic results that follow oral therapy are comparable in every way to those following parenteral therapy in pneumococcic pneumonia, in gonorrhea, in tonsillitis, scarlet fever, erysipelas, acute otitis media due to hemolytic streptococcus, in Vincent's stomatitis and pharyngitis and in staphylococcic infections of the skin and subcutaneous tissues such as abscesses, carbuncles, furuncles, impetigo, etc. Oral therapy has another advantage in that hypersensitive reactions are less frequent than following parenteral therapy.

In the prophylaxis of gonorrhea it has been shown that one tablet of 250,000 units taken within two hours after exposure will usually prevent infection.

Dosage schedules that have been effective in the treatment of various diseases have varied greatly. In general it can be said that three to five times the minimum effective parenteral dose of penicillin has been used with a favorable result. They may be summed up as follows: Pneumococcic pneumonia, 600,000 to 1,000,000 units daily, 150,000 to 200,000 units daily in infants and children; gonorrhea, 200,000 to 500,000 units for one day; hemolytic streptococcic infections, 450,000 to 1,000,000 units daily for five to seven days; staphylococcic infections of the skin, 1,000,000 units a day for five days; Vincent's stomatitis, 400,000 to 600,000 units a day for three to four days.

CARINAMIDE

Carinamide has been used as an adjunct to penicillin therapy in order to delay its excretion by the kidney. This drug acts by inhibiting the excretion of penicillin by the renal tubules. It has been found that when 2 to 4 Gm. of carinamide are given by mouth every three or four hours the plasma concentrations of penicillin can be increased two to thirty-two fold over those obtained when the same amount of penicillin is given intramuscularly with carinamide.

This form of combined therapy has been most useful in dealing with patients who have infections due to highly resistant organisms such as are seen in occasional cases of subacute bacterial endocarditis or staphylococcic sepsis. Thus following a single injection of 500,000 units of penicillin intramuscularly and 3 Gm. of carinamide orally, plasma concentrations varying from 28 to 34 units can be maintained for a three hour period. Carinamide has been recommended by Boger and Flippin¹¹ as a valuable agent when more than 500,000 units are required daily for the treatment of any infection.

PENICILLIN DUST (INHALATION OF CRYSTALLINE PENICILLIN G)

In an attempt to treat a variety of infections of the respiratory tract, methods have been developed for inhalation of penicillin dust directly into the respiratory passages. This method of treatment was first described by Krasno, Karp and Rhoads.¹² It has been used most extensively in the treatment of patients with bronchiectasis and other chronic infections of the respiratory tract. Infections of the upper part of the respiratory tract have also been treated in this manner. In general it can be said that following the inhalation of 100,000 units of penicillin dust there is good evidence that penicillin is absorbed. Maximum levels of penicillin in the blood plasma are obtained one hour after inhalation and penicillin can be detected for three to five hours after inhalation. Cultures of the nose, throat and sputum following such therapy show a

decrease in the bacterial population and in particular of the gram-positive bacteria. Hypersensitive reactions have been reported in from 3 to 6 per cent of patients. They are characterized by local reactions in the mouth and throat or at the point where penicillin comes in contact with the skin so that patients complain of stomatitis and irritation of the posterior pharynx and skin. Systemic reactions are infrequent. This form of penicillin therapy is easily available for use in office and home practice. It is usually recommended that at least one to three inhalations of 100,000 units of penicillin dust be used daily.

REFERENCES

1. TOMPSETT, R., TIMPANELLI, A., GOLDSTEIN, O. and McDERMOTT, W. Discontinuous therapy with penicillin. *J. A. M. A.*, 139: 555, 1949.
2. WEISS, W., and STEINBERG, I. Treatment of pneumonia with intramuscular aqueous penicillin once a day. *Am. J. M. Sc.*, 217: 86, 1949.
3. PRICE, A. H. Aqueous penicillin therapy for pneumococcal pneumonia. *J. A. M. A.*, 138: 292, 1948.
4. STOLLEMAN, G. H., ROSTON, E. H. and TOHARSKY, B. A guide to the use of procaine penicillin in hospital practice. *New York State J. Med.*, 48: 2501, 1948.
5. HEWITT, W. L., WHITTLESLEY, P. and KEEFER, C. S. Serum concentrations of penicillin following administration of procaine penicillin G in oil. *N. England J. Med.*, 239: 286, 1948.
6. KITCHEN, D. K., THOMAS, E. W. and RICE, C. R. Serum concentrations following five treatment schedules with procaine penicillin in oil with aluminum monostearate. *J. Invest. Dermat.*, 12: 111, 1949.
7. ROBINSON, J. A., HIRSH, H. L. and DOWLING, H. F. Oral penicillin in the treatment of various bacterial infections. *Am. J. Med.*, 4: 716, 1948.
8. BURN, P. A., McDERMOTT, W., HADLEY, S. J. and CARTER, A. C. The treatment of pneumococcal pneumonia with orally administered penicillin. *J. A. M. A.*, 129: 320, 1945.
9. GYORGY, P., VANDEGRIFT, H. N., ELIAS, W., COLLIS, L. S., BARRY, F. M. and PILCHER, J. D. Administration of penicillin by mouth. *J. A. M. A.*, 127: 639, 1945.
10. FINLAND, M., MEADS, M. and ORY, E. M. Oral penicillin. *J. A. M. A.*, 129: 315, 1945.
11. BOGER, W. P. and FLIPPIN, H. F. Penicillin plasma concentrations. *J. A. M. A.*, 139: 1131, 1949.
12. KRASNO, L., KARP, M. and RHODES, P. S. Inhalation of penicillin dust. *J. A. M. A.*, 138: 344, 1948.

Clinic on Psychosomatic Problems

Psychogenic Deafness in a Disturbed Boy

THE clinics are designed to bring out psychosomatic relationships both in symptomatology of the patient and in the organization of the hospital. Reports are directed by Drs. Stanley Cobb and Allan M. Butler, and are edited by Dr. Henry H. W. Miles. This is a report of a conference of the Children's Psychiatric Service of the Massachusetts General Hospital. The preparation of these psychosomatic case histories receives support from the Josiah Macy, Jr. Foundation.

DR. PETER H. KNAPP: The patient (No. 540858), a nine year old boy with hearing loss, came to us through the Ear, Nose and Throat Clinic. A program of lip reading and the fitting of a hearing aid had been advised but before proceeding with the rehabilitation plan the boy's evaluation as a behavior problem had been requested. On looking over his clinic record it was noted that eighteen months previously the audiogram had disclosed only a mild left-sided hearing loss. Subsequent tests had shown loss also on the right but of a suspiciously variable and inconsistent type. Accordingly our first step was to create a friendly relationship with the boy and to re-test him. This time the audiogram was completely normal on the right, proving that he had no actual acoustic loss in that ear and that he needed not hearing rehabilitation but psychologic investigation. The mother began to bring the boy regularly to the Child Psychiatry Clinic. We will now hear the social history.

MRS. MARJORIE SPRINGER: The patient's background is a disturbed one. The mother married at nineteen when she was already three months pregnant. She never lived with her husband and was divorced from him when the patient was a year old. The father is a physician who was in the Army at the time they were married and who now practices in a western state.

After the birth of the boy the mother returned to live with her family of which the dominant figure was her mother, a stern, irritable widow. A nervous married sister, two older brothers and a twin brother were

sporadically present in the household. There was no permanent male figure in the family group. During the patient's infancy his mother was moody and depressed and the grandmother took over many of the maternal functions. The boy was in many ways quite dependent; for example, he was fed by the grandmother until he was seven years old. Despite this he attempted to fulfill a man's duties as best he knew how, trying particularly to be comforting and protective toward his mother in the increasingly frequent bitter quarrels between her and the grandmother. With his conflicts he remained emotionally dependent upon these females and was very insecure socially. He wondered about his father's unexplained absence and, not being told the true facts, developed an elaborate set of fantasies about him. Finally about a year ago his mother told him that the father would not come back eventually as the patient had wished.

The boy has always been a restless, hyperactive child and at the age of two and one-half he was described as being "inattentive" in nursery school. A factor in his insecurity may be found in the mother's periodic desire to place him in a foster home. The mother told of other incidents which seemed related to the patient's insecurity. When he was three years old he was taken to a doctor for an infected arm, was hurt by the doctor's manipulations and seemed to believe that his mother had betrayed him. At six years an even more traumatic experience occurred. He had a tonsillectomy at home. There was a long frightening wait for the surgeon to arrive and a violent

struggle before the boy could be anesthetized. Besides the tonsillectomy, a tooth extraction was done which the boy had not expected.

Following the operation a slurring of speech developed and shortly thereafter difficulty in hearing which was intermittent, variable and seemed to the mother to represent inattention. It was also about this time that the mother received the attentions of a man who was openly critical of the boy and urged her to place him in a home. The patient at this time became rebellious and quarrelsome, and his symptoms of speech and hearing difficulties grew more severe until he was finally taken to the Ear, Nose and Throat Clinic for examinations. As Dr. Knapp has mentioned, it was at first thought that his behavior problems were secondary to the loss of hearing.

My contacts with the mother were for the purpose not only to obtain historical data but also to find out about her own problems. At first she expressed much resentment toward the boy, believing that he interfered with her chances of happiness, and she expressed the desire to place him in a foster home. By the second interview, however, this desire seemed less intense. She intended breaking off her relationship with the man who, she said, did not want the boy and did not even seem to want her very much. In subsequent interviews she talked more realistically about her son and in response to encouragement in that direction expressed an increasing amount of warm feeling for him. She displayed more and more resentment toward her mother and began to think of leaving the latter's home. Although still far from emancipated, the boy's mother seems to be more comfortable, apparently as a result of her relationship to us in the clinic, and she is pleased with the boy's progress.

DR. KNAPP: The patient has been seen in ten psychotherapeutic interviews of about forty-five minutes each. The first of these served to clarify facts in the immediate history and to make friendly overtures to the boy. By the Goodenough test his in-

telligence appeared to be well above average. After the first session there was a lapse of a month because of the mother's reluctance, and then interviews were resumed at weekly intervals.

The second time he came he was friendly and very talkative, telling how he and a friend had devised a "time machine" to transport themselves into the future; they were worried, however, how to get back to the present. The patient closed with an expression of resentment against physicians mentioning his tonsillectomy and saying: "A doctor made me suffer."

He started the next session talking about a newspaper he was planning to publish on his printing press and mentioned how he played "junior commando" with a friend, going off into fantasy about how they could drop from trees onto their enemies. We played a game of checkers, the patient first insisting that there should be "no losing on purpose." He lost.

The fourth interview was begun by a request to see a laboratory which he might write up for his newspaper. He then produced some gory antivivisectionist literature and talked with abhorrence about cruelty to animals. Next he spoke more about his plans for a gigantic newspaper although he was having trouble with his neighborhood staff of twenty-five contributors. As he talked on he suddenly grew fearful, came very close to me and said that sometimes he felt like killing himself because there was a gang of bullies in the neighborhood. He would not say more but changed the subject and asked to play checkers. It was a closer game but again he lost. We ended the interview by going to see a nearby laboratory where he scrawled profuse notes for his newspaper article.

Next week he was in the laboratory before the hour, being shown around by a technician. The session began with a game of Chinese checkers which he taught me; this time I was deliberately clumsy, still he just managed to lose. During the game he commented on the heavy boots I was wearing, "just like the boots Boris Karloff wore in

'Frankenstein's Child'." He told of writing to Hollywood, asking to play that role. "If I was his child, I'd be as big as I am now when I was born, and when I grew up—whew!" A little later in the game he said: "Boy, how I love to be beaten up, I mean beaten." After the game he was very restless and searched through a card file, asking if there were a "Dr. Arthur" in the hospital. His father was a doctor, he said. "They say he's out West, but I think he's right here in this hospital somewhere." He said he would never want to be a doctor, adding, however, that it would be interesting to know how to stop bleeding. At the end he expressed some resentment at having to come every week. He was encouraged to speak about his anger and urged to try weekly appointments at least once more.

During the sixth interview there were two innovations. The first was a small brown mongrel puppy which the patient had brought to the clinic, telling me that it was a female, but later referring to it by mistake as "he" and imagining the friendly little animal to be a huge, strong watchdog. The second innovation was a complicated game of checkers, devised by the patient, involving repeated crowning of Kings until eventually all that remained were two high towers of checkers. In order to terminate an endless game I let the patient win. At first he was intensely anxious but then he recovered, made me put away the checkers, as loser, and playfully threatened to strike me with a chain.

Next time, still bringing the dog, he wanted to switch seats with me and then spontaneously suggested starting our "weekly conversation." With considerable agitation he went on to talk about his mother, her demands on him, her occasional irritability and above all her quarrels with the grandmother which would make the mother cry and disturb him greatly. "*Sometimes I even try not to hear her.*" He spoke about his fear that the women in the house would get rid of the dog and seemed reassured when I mentioned that I would take the matter up with the social worker. In a further effort

to offer support and identification I suggested that a man had to get away sometimes and that possibly it might help if he were to get off by himself a little more. At the end of the interview he grew alarmed that his mother might be able to hear him talking through the walls.

He started the eighth visit by saying: "Hi, pal," then apologized for the remark. After a preliminary game he again turned to the subject of his mother and once more showed a mounting anxiety. He spoke of how she yelled at him: "You know how women are." At one point he suddenly asked to be hypnotized; then next week he could tell me everything. The dog again figured prominently. He was worried about my suggestion of housebreaking her; he was going to hypnotize her; he put her ears back make her "look like a girl." He also tried putting his ear against the wall to find out whether this time he could hear his mother. He talked more about the situation at home, expressing concern over his mother and fear of leaving her. In closing he drew a picture of two roads, one straight stretching into the distance and one curving, coming to a dead end. He said: "I've got to decide which one to take."

Next week for the first time he seemed much quieter. He was to go to the dentist. Discussion of that led to a few more recollections about his operation. Suddenly he began drawing pictures of anger and death. He then asked whether I had a dictaphone. His suspicion and anxiety gradually diminished; he grew very friendly and talked enthusiastically about his new hobby, stamp collecting. On opening the door to leave the interview, he saw his mother in the hall and accused her: "You were listening."

In the tenth and last interview prior to the conference, we talked about the possibility of his appearing before the group. There was more talk about cruel doctors and about hypnotism. Now he wanted me to teach him hypnosis so that he could hypnotize his enemies and make them wake up friends. Again there was a spirited discussion of stamp collecting, as well as the

patient's enthusiasm for the antivivisection movement. He was distracted by the noise of a girl crying next door and stated his wish that the room were sound-proof. We parted on amiable terms and he expressed pleasure that his mother was not to be allowed at the conference.

PRESENTATION OF PATIENT

The patient was a wiry boy, very tall for a nine-year old, who was tense and physically overactive. He had been playing with a stethoscope, pretending to listen to his heart, and was embarrassed when the doctors saw him with this instrument. He spoke readily to the group but rather incoherently, the words tumbling out in a slurred way, expressing some fear and distrust of doctors in general. He was permitted to leave the room after a very brief appearance.

DISCUSSION

DR. KNAPP: In cooperation with the Ear, Nose and Throat Clinic we have been interested in the emotional aspects of deafness. We have found not only a considerable number of patients who were emotionally disturbed by their organic hearing defect but also a number in whom the primary difficulty was psychologic. So far there have been eight such cases of hysterical deafness, all of them in children. The problem, then, is by no means rare.

In presenting the case this morning I am anxious to get suggestions as to how to proceed with therapy. It seems to me that the problem is one of tremendous anxiety over growing up and uncertainty over assuming the role of a man.

DR. GEORGE CARTER: I am not sure about the mother's brother who lives with the family and is never mentioned by the patient. Is he living with them at the present time?

MRS. SPRINGER: He moved away about four months ago. The mother says that he was never a key figure in the household. Apparently he never played much with the boy and their relationship was never warm.

DR. KNAPP: The whole situation was so insecure without a father that everything has constantly conspired to drive this boy back to a state of frightened dependence on his mother, and any attempted independence seems to threaten him with losing her and to make him fear men. It would seem that disparaging remarks were often made about the absent father and thus he became a threatening figure. I should imagine that the tonsillectomy especially mobilized the fears of being mutilated and emasculated; and those fears now are very much present. I have thought that the therapeutic endeavor should be to establish a good relationship with him. Actually, with his readiness to talk one could go even further and get at the content of these fears and show him that he can grow up and still keep his mother's love and lose his fear of men. We must, however, go slowly as any mention of an operation still makes him extremely anxious. It is encouraging that he seems to want to talk about his fears and in two or three months it may be possible to deal with them. The parallel question that I would like guidance on is the question of the management of the mother because she is really in a bad situation. I think that her warm relationship to the social worker is most encouraging. We hope that she will be able to emancipate herself, set up a separate establishment and eventually make a secure independent adjustment.

DR. SAMUEL KAPLAN: I agree with Dr. Knapp's formulation of the boy's general problem. It is interesting that as far as we know this boy showed no overt difficulties in the home until the age of five. It is my belief that he must first work through the problems of being a little boy before we push him into the problems of growing up.

DR. CARTER: I am always a little confused by the use of the term "castration" as occurring in this particular situation. Obviously, the boy *does* have fears of being hurt and is afraid of hostility from the outside world. Yet, I am not quite convinced of the castration formulation and wonder about

his ambivalence in the matter of laboratories. He does not want to see animals hurt yet he wants to see where the animals are operated upon. He does not know what his role should be.

DR. KNAPP: I agree that we have no precise evidence for fears of castration but we have got evidence, I think, of his ambivalence as to what role he is going to play—the big, strong, powerful man or the role of a feminine person. You will recall his thoughts about Frankenstein's child, and how large he would be when he grew up and then contrasted with that his remark: "How I love to be beaten up." That slip of the tongue was probably not insignificant.

DR. LUCIE JESSNER: What is the grandmother like?

MRS. SPRINGER: The grandmother is sixty-five years of age, apparently in good health. She is the one who manages the household, always pays the bills and pays the rent. The mother does not even know how much the rent is. She turns over a certain amount of her pay to the grandmother who controls everything.

DR. CARTER: Would the mother be able to afford a separate home?

MRS. SPRINGER: Yes, she makes quite a good salary at the present time. Some of the mother's siblings are contributing to the grandmother's support so she can be relieved of her responsibility there.

DR. NICHOLAS D. RIZZO: I would like to ask Dr. Knapp what in his opinion was the boy using his hearing loss for?

DR. KNAPP: I do not know, except for the superficial part of it, namely, to avoid hearing unpleasant things, so to speak. In one interview in talking about the quarrels which upset him a great deal, you will remember he said: "Sometimes I even try not to hear." What the deeper meanings are I do not know. He was sent home from school originally because of his hearing loss. It seems to be tied up with the passive role he is impelled to play, namely, cutting himself off from contact with people, from activity and growth which to him are laden with anxiety.

DR. RIZZO: It is interesting that the speech difficulty was one of the reasons why the patient was referred earlier to the hospital, and his speech here before the group is similar to that of children with genuine hearing loss.

DR. EDNA SOBEL: It would seem that the tonsillectomy, hearing loss and fear of operation are linked together.

DR. GERTRUD REYERSBACH: Does it not seem that presenting a child before a group is rather a dramatic experience for him and that he may not respond the way he feels? For example, a child when asked how he is, usually answers that he is fine. At least I have generally found it so.

DR. KNAPP: In this case the boy was so eager to come and so willing to show off in a crowd that I thought he would be able to respond well.

DR. REYERSBACH: But does not bringing children into staff conferences damage the relationship between the child and the psychiatrist afterward?

DR. KNAPP: I think you are right. However, in certain cases if the preparation is good and the relationship is warm, it may be turned into a source of pleasure for him, especially in this case in which the boy was proud to think that he was important enough to come in.

DR. JESSNER: That is an interesting question since this is a very dramatic experience for a child. However, we believed that it was important for the group to see the child.

DR. SOBEL: I wonder about the hearing loss being used to cut himself off from people whom he seems to fear?

DR. JESSNER: I think his hearing is an area in which he has been tremendously frustrated. He did not hear about his father, and knows that he was kept in the dark about him for a long time. Also he did not hear in advance that his tooth would be taken out. I think that a great deal of resentment is connected with what he *does hear* and what he *does not hear*. It is encouraging that he now pays more attention to what is said in general. He did not want to hear the demands of the grandmother or to hear

in school and was not particularly anxious to hear what he *should*; in contrast, he heard only what he *wanted to hear*. I believe that by showing him the laboratory and the animals you are letting him express many of his fears. He thinks something must have been done to his body, that some function has changed so that he cannot speak and cannot hear. The fear of being mutilated is extremely strong. In the whole area of the hearing there is still much that he wants to hear, and his fantasies about his father, who is a doctor, are very important. I would give him an opportunity to talk about his father, and Mrs. Springer might sometime in her discussion with the mother find out how much he knows about the father. He has a great deal of feeling about antivivisection and when he mentions animals, he may be actually talking about himself. I would let him talk a great deal about what he thinks is done to the animals. One would get his castration fears in that form, because he must very definitely believe that he is treated like an animal to which something was done. I think, also, that his idea about hypnosis is quite important and that he believes he could tell everything about his mother through hypnosis. I wonder whether one could not explain to him the ambivalence of his feelings and that it is natural to have love and hate together. You could perhaps side with him against women at times and let him express all that he hears about animals and what he hears in regard to men. I also have a feeling that it is quite characteristic that he calls you "pal" and tries to be your equal, not only to identify himself with you but to be on an equal footing as a grown man.

FOLLOW-UP NOTE

One year after conference the boy was seen approximately thirty times. Symptomatically he was improved. His behavior at home was much better and he was doing well at school. Deafness was not a complaint although when tested at the start of the fall term he still showed some hearing loss. He described the testing afterward saying that

"some kids pretend to hear worse than they do," which was strong evidence that in some way he was himself aware of a tendency to relapse when attention was focussed on his ears in a test situation. He continued to talk about the acoustic area, speaking of his interest in radio programs, sound effects, and once putting on a ventriloquism act in which he played the part of a doctor taking care of a small patient. The importance of doctors and operations to him had been strikingly borne out by his play material. He had acted out a violent scene in which he again took the role of physician, slashed open the neck of a toy lion, talked of the risk of death from a blundering surgeon, removed "two jelly beans" and finally killed the animal. Other verbal and play productions suggested that there was a strong desire to use the psychotherapist as a model for behavior but that he was afraid of what might happen if he were to become a powerful man, whom he inevitably imagined as cruel. An effort was being made to make him clearly aware of this conflict. In that way it was believed that it might be possible to cement the symptomatic improvement, which so far depended upon continued relationship with the therapist.

A similar development was taking place in the mother who believed that the boy had "grown up a lot." She was reasonably well as long as she was in contact with the social worker. However, she was still struggling to achieve a permanent solution for her own conflicts in relation to remarriage and to her mother, which would leave her truly independent.

INTERPRETATION

Part of the discussion was in terms of psychoanalytic theory and there was some difference of opinion regarding the concept of "castration anxiety." We mention this specifically only to say that in this case terminology is unimportant. The significant points to be noted by the pediatrician, otolaryngologist or general practitioner not conversant with dynamic psychiatry can

be seen clearly by a little reading between the lines of the interview material. The temporal relationship between the tonsillectomy and onset of speech and hearing difficulties is striking. The great anxiety in the boy's mind in regard to being hurt is evident, appearing over and over again in the interviews. According to psychoanalytic theory, further investigation and elaboration of the patient's fantasies would ultimately disclose fear of loss of the penis; for the physician who is primarily interested in making the proper diagnosis and directing the patient toward appropriate therapy it is sufficient to recognize the fact that the fears of bodily injury or mutilation are important.

The dynamic structure of the problem in an oversimplified scheme can be seen as follows: Without a father and in the face of great insecurity, the boy was forced into a dependent attachment to his mother. The father was a physician and we know that the boy heard disparaging remarks about him. It would not be taking a long step to suppose that the little boy feared this absent, threatening, doctor father. (He resented his father's desertion, and hostility in a child's mind is associated with fears of reprisal.)

Thus when operated upon and particularly when something was done to him without warning, the patient's *fears* of mutilation were demonstrated to him as *reality*. It is very probable that in his fantasies, "doctor" and "father" were equated, both being fearful and cruel persons.

The treatment process was presented in some detail to illustrate the teamwork of psychiatrist and social worker. In psychotherapy with children it is advisable, if not imperative, that the mother be helped to understand her own problems, since it is so often in the mother-child relationship that the roots of the trouble lie. The interview

material may have seemed diffuse and incoherent. One must remember that in dealing with children a full and connected story cannot be obtained, and one depends to a large degree upon indirect evidence based upon the child's actions, fantasies, hobbies, artistic productions, etc. For example, this boy's fears of being injured or mutilated are revealed obliquely in his preoccupation with vivisection.

In psychiatric work with children it is by no means uncommon to see problems involving fears of bodily injury activated or intensified following an operation. It is now generally accepted that tonsillectomy (or other operative procedure) should be postponed, unless there are urgent indications, until the child is at least eight years old. When an operation has to be done, the patient should be prepared by telling him in advance what will happen, by giving adequate reassurance, having his mother with him when he awakens from the anesthesia, etc.

As this case illustrates it may not be necessary to analyze in detail all the ramifications of the child's conflicts. The satisfactory therapeutic result was probably due to: (1) the secure relationship which the boy developed with the male therapist who provided a satisfactory masculine figure with whom to identify, and (2) the increased warmth and affection which his mother was able to give him, achieved through her contacts with the social worker.

The question of a specific diagnosis was not mentioned. The neurotic problems of children usually do not fit the conventional clinical patterns which are described for adult psychoneurosis. From a practical standpoint, certainly, the attaching of a descriptive label is far less important than an understanding of the dynamic mechanisms of the illness.

Clinico-pathologic Conference

Cardiac Failure, Elevated Basal Metabolic Rate and Psychosis*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, A. S., (No. 156162), was a white, married housewife, fifty-six years of age, who entered the Barnes Hospital for the first time on January 4, 1948, complaining of "a sensation of choking" and dyspnea on exertion. The family history was of interest in that her father and one brother had had heart disease. Four of her father's immediate relations had had "a goiter" and one of them had been subjected to surgery.

Three times during her childhood the patient had pneumonia. When she was twenty-two, six months after her third pregnancy, she developed pain in the left chest and a cough which lasted three weeks. She apparently recovered from this illness and was well until the age of thirty-five at which time she had "a nervous breakdown" which lasted several weeks; its onset followed shortly after the birth of her eighth child. At the age of forty-nine she received a series of injections of an unknown type for marked stiffness of the joints of her left hand, and when she was fifty-four she developed soreness and stiffness of her shoulder joints.

During her sixth pregnancy the patient became aware of enlargement of her neck. Concomitantly she had the first of a series of "choking sensations" which she could not further describe except to state that she was relieved when she lay flat in bed. Similar episodes occurred in each of her four succeeding pregnancies and occasionally between them, but the size of her neck did not

change since she first noted it to be enlarged. One year before entry the patient noted onset of dyspnea on exertion as well as of paroxysmal nocturnal dyspnea. The nocturnal attacks began to appear with increasing frequency and the patient developed a dry, annoying cough. Two weeks before entry her ankles swelled and she was forced to wear rubber stockings. The attacks of paroxysmal nocturnal dyspnea became so severe that she was forced to sleep sitting up in a chair. She was seen by a physician who told her that she had "an inward goiter" although at no time had she experienced difficulty in swallowing. Although her appetite had been good, she had had no evidence of excessive nervousness. During the four years prior to admission she had lost 28 pounds in weight and had noted increased ease of fatigability but at no time did she perspire excessively nor had she had precordial pain. Three weeks before she came to the hospital her physician prescribed 15 drops of a bitter, dark liquid to be taken every four hours. She took this preparation for two weeks. When she was seen in the out-patient clinic several days before admission, she was advised to take digitoxin instead of the liquid medicine.

At the time of entry her temperature was 38.2°C., pulse 100, respirations 24 and blood pressure 180/96. The patient was well developed and well nourished but because of dyspnea she sat propped up in bed. The skin was smooth and of fine texture but no

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

perspiration was apparent. There were many varicose veins over both legs. The pupils reacted normally to light and accommodation and the fundi showed only mild sclerosis of the vessels. There was no lid lag, stare or inability to converge. The mouth was edentulous. A large, firm, slightly nodular mass was present on the right side of the neck anteriorly and its lower border could be defined above the clavicle. The thyroid isthmus was palpable and the left lobe of the thyroid gland was barely discernible. There was no bruit. The trachea was in the midline. The neck veins were dilated and engorged, particularly on the right. Examination of the lungs revealed them to be clear to percussion and auscultation. The left border of cardiac dullness was 11 cm. to the left of the mid-sternal line in the fifth interspace. There was slight right border enlargement. A loud, harsh grade III systolic murmur was heard at the aortic area but it was not transmitted. A grade II early diastolic murmur was heard over the aortic area and along the left sternal border. P_2 was accentuated. At the mitral area there was a grade II systolic murmur and a low pitched rumbling mid-diastolic murmur which was heard best when the patient lay on her left side. There were no thrills. The rhythm was regular and the sounds were of good quality. The liver edge was palpable 4 cm. below the right costal margin and was slightly tender. The spleen could not be felt. There was 1+ pitting edema of the lower extremities. The patient exhibited no tremor of the outstretched hands and the neurologic examination was within normal limits.

The laboratory data were as follows: Blood count: red cells, 4,580,000; hemoglobin, 14.5 Gm. per cent; white cells, 9,800; differential count: eosinophiles, 1 per cent; stab forms, 3 per cent; segmented forms, 75 per cent; lymphocytes, 19 per cent; monocytes, 2 per cent. Urinalysis: albumin, trace, otherwise negative. Stool examination: negative. Blood Kahn test: negative. Venous pressure: 225 mm. of saline. Circulation (decholin) time: 21 to

28 seconds, (end point not definite). Blood chemistry: non-protein nitrogen, 22 mg. per cent; total protein, 6.0 Gm. per cent; albumin, 3.8 Gm. per cent; globulin, 2.2 Gm. per cent; chlorides, 105 mEq./L.; icterus index, 14 units; cephalin-cholesterol flocculation test, negative; thymol turbidity test, 1.9 units. Roentgenogram of the chest: "There is second degree cardiac enlargement. The aorta is tortuous and there are increased lung markings suggestive of pulmonary vascular congestion." Electrocardiogram: ST segment slightly depressed in leads I and II, T waves biphasic in leads I and II and inverted in CF_4 .

Two days after entry the attending physician described a systolic thrill over the aortic area. Otherwise the signs were unchanged except that the patient had become afebrile. She was completely digitalized, was given diuretics and placed on a low salt diet. Fluoroscopy with a barium swallow did not reveal left auricular enlargement. After the patient had achieved compensation the basal metabolic rate was +55. The blood cholesterol was 218 mg. per cent. On the tenth hospital day the patient was ambulatory. During the ten days she had lost 9 pounds in weight. The cardiac signs were as on entry except that the mitral diastolic murmur could no longer be heard. A radioactive iodine excretion test was performed and it was found that 80 per cent of the ingested dose was excreted. Just prior to discharge on March 13, 1948, the mitral diastolic murmur was again heard, sharply localized over the apex. The patient left the hospital to follow a therapeutic regimen designed to preserve her cardiac status; in addition she was given potassium iodide.

Following discharge she was seen regularly in the endocrine clinic. One month after she left the hospital, during which time she had taken potassium iodide steadily, her basal metabolic rate was found to be +48. Prophylthiouracil therapy was instituted, a dose of 50 mg. five times a day being given. When she returned to the clinic on May 23rd, she had gained 1½ pounds

in weight. She was given mercurhydrin and sent into the hospital that day.

At the time of entry her temperature was 38°C., pulse 84, respirations 24 and blood pressure 140/80. The significant changes in physical findings from the first admission were as follows: The trachea appeared to be pushed to the left. The systolic thrill over the aortic area was easily palpable when the patient sat erect and the aortic systolic murmur was now transmitted to the neck. The rumbling, low pitched, mid-diastolic murmur at the apex was easily audible and there were a few rales at the lung bases. The liver was enlarged and there was moderate peripheral edema.

The laboratory findings were normal with the following exceptions: The urine showed 2+ albuminuria. The venous pressure was 235 mm. of saline, the circulation time with decholin, 24 to 27 seconds. The non-protein nitrogen was 24 mg. per cent, the basal metabolic rate +22, the blood cholesterol 202 mg. per cent.

The patient was again treated for cardiac decompensation; she improved rapidly, becoming asymptomatic in several days. She left the hospital on May 29, 1948, to be followed in the clinic. She was seen in the endocrine clinic on June 10th and was given 10 mc. of radioactive iodine. She remained quite well for two weeks; then once again dyspnea on exertion appeared. Three days before her third admission dyspnea became marked and the onset of orthopnea was noted. She was re-admitted on July 10, 1948. Her temperature was 38.2°C., pulse 44, respirations 22 and blood pressure 170/100. The physical findings were essentially the same as on the second admission. The laboratory findings likewise were unchanged except that the patient now had 3+ albuminuria.

On the second hospital day the patient was noted to have an apical rate of 48 with runs of extrasystoles. An electrocardiogram revealed frequent premature ventricular contractions with bigeminy. The basal metabolic rate was +19 and reduction in the size of the right lobe of the thyroid

gland¹ was noted. When she left the hospital on July 15, 1948, no further therapy for thyrotoxicosis was prescribed. About five weeks after discharge on August 21st the patient was seen in the clinic at which time her basal metabolic rate was +40. At that time she was given 5 mc. of radioactive iodine. When she returned on September 21st her basal metabolic rate had risen to +47. During the interval she had done well but just before returning to the clinic she had a rather sudden re-appearance of dyspnea and recurrence of edema. She had continued to take digitoxin, to follow a low salt diet and receive mercurhydrin regularly in the medical clinic. She was re-admitted for the last time on September 21, 1948.

Physical examination revealed the temperature to be 37.8°C., pulse 64, respirations 32 and blood pressure 130/85. The patient was now poorly nourished, appeared chronically ill and was markedly dyspneic. The right lobe of the thyroid gland measured approximately 3 by 4 cm. The trachea was deviated to the left. There was impaired resonance to percussion over the right base and rales were heard in this area. Cardiac examination was unchanged. There was 3+ pitting edema of the legs.

Laboratory data were as follows: Blood count: within normal limits. Urinalysis: albumin, 2+, centrifuged sediment, 20 to 30 white cells, occasional red cells and hyaline casts per high power field. Blood chemistry studies: within normal limits. Blood cultures: negative. Electrocardiogram: ST segments depressed in leads I, II and CF₄; PR interval 0.19; T waves inverted in leads I, II, and CF₆; occasional ventricular premature contraction; left axis deviation. Venous pressure: 182 mm. of saline. Circulation time: 50 seconds.

The patient was fluoroscoped and the heart was noted to be greatly enlarged both to the right and to the left. It was boot-shaped in contour. A barium swallow indicated slight enlargement of the left auricle. On the third hospital day the patient's temperature rose to 38.4°C. The chest signs remained unchanged. A chest x-ray re-

vealed small rounded areas of infiltration at the right base considered to represent early pneumonia. Penicillin therapy was instituted. One week after admission the patient suddenly became markedly disoriented and exhibited definite paranoid trends. Sometimes she was uncommunicative and at other times agitated. During the second week of the hospital stay she became even more disturbed. A lumbar puncture was performed and an initial pressure of 220 mm. and a final pressure of 145 mm. of water were recorded. The spinal fluid findings were entirely negative. The patient exhibited periods of delirium and on careful questioning her family stated that she had behaved abnormally on occasions just before her admission. A psychiatric consultant was called and made diagnoses of delirium, unstable personality and paranoid tendencies. The patient continued to have a slight elevation of temperature. Repeated blood cultures were negative and significant numbers of red cells did not appear in the urine. By the end of the third week, although the patient's cardiac status had markedly improved, she became more difficult to manage and was transferred to the neuropsychiatric service. On the next day her temperature rose to 39.6°C., her white count to 26,400 and the differential count showed 92 per cent segmented forms. She became semicomatose and was transferred back to the medical service.

Physical examination revealed definite signs of consolidation of the right lower lobe and streptomycin therapy was instituted. Penicillin had been continued throughout this previous period. Further blood cultures were negative. Sputum examination revealed cocci and chains in pairs. The non-protein nitrogen had risen to 80 mg. per cent. The chlorides were 96 mEq./L. and the icterus index 30 units. Sodium bilirubinate was 1.9 mg. per cent, the bilirubinglobin 1.9 mg. per cent, with a total of 3.8 mg. per cent. Because the diagnosis of pulmonary infarction was seriously considered, dicumarol therapy was begun and the prothrombin time was lowered to 30 per cent

of normal. On October 15th, about three and one-half weeks after entry, the patient's icterus index had risen to 40 but jaundice was not clinically discernible. Although the patient became more alert and her strength increased, her psychotic state again became pronounced. During the fifth week her temperature which had fallen to normal again began to spike despite the fact that she was still receiving both streptomycin and penicillin. At this time her icterus index was 24 units. The heart sounds became weaker and the blood pressure fell somewhat. The pulmonary signs were unchanged but her white count had fallen to 11,400. Sputum cultures were positive for coliform organisms. Edema of the ankles increased and there was marked calf tenderness. The patient's agitation became extreme and it was very difficult to control her. Just before she died she had periods of transient auricular fibrillation. She became unresponsive and expired quietly on October 27, 1948.

CLINICAL DISCUSSION*

DR. W. BARRY WOOD, JR.: The resident has chosen an extremely difficult and complicated case for discussion today. In our discussion we must consider the cardiovascular system, the thyroid gland, the pulmonary lesion and finally the psychosis which made management of this patient so difficult for the house staff. Since the cardiac disease probably represents the most straightforward aspect of this case, it might be well to begin with that phase of this patient's illness. Mr. Lund, would you discuss the nature of the cardiac involvement?

MR. ROBERT H. LUND: The duration of the patient's illness and the physical findings suggest that she had aortic stenosis and aortic insufficiency. Whether she had mitral stenosis is not as clear to me although I think it is entirely conceivable that the mitral valve was involved.

* It should be noted that this clinico-pathologic conference differs from those usually published in the Journal in that the discussion was carried on by students selected from the Senior class rather than by members of the faculty.

DR. WOOD: To what etiologic factor do you ascribe aortic stenosis and insufficiency?

MR. LUND: I believe this patient had rheumatic heart disease. There is no history of acute rheumatic fever but its absence does not particularly disturb me in making such a diagnosis. One must also consider arteriosclerosis of the valve in passing, but no mention was made of calcification of the aortic valve in any of the x-rays; the fact that no calcification was described does not rule it out.

DR. WOOD: Mr. Roscan, do you expect the pathologists to demonstrate calcium in this patient's valve?

MR. MARVIN ROSECAN: Yes, Dr. Wood, I do. A series of 107 cases of aortic stenosis was recently reported by Kumpe and Bean;¹ calcium was demonstrated in the aortic valve at autopsy in every one of the 107 hearts.

DR. WOOD: That was indeed a most striking finding. The monograph to which you refer is an excellent review on all aspects of aortic stenosis and as you point out every one of the hearts studied by the authors showed calcium in the aortic valve at autopsy either grossly or microscopically. Thus one would certainly be on safe grounds if he states that the pathologists will demonstrate calcium in this patient's valve. You agree then with Mr. Lund's preliminary diagnosis.

MR. ROSECAN: Yes, I do.

DR. WOOD: Let us assume then that this patient probably had rheumatic heart disease with calcific aortic stenosis. Mr. White, what about mitral valve involvement?

MR. LAURENS T. WHITE: It is entirely possible that this patient will have no actual mitral disease. Again in their monograph on aortic stenosis, Kumpe and Bean included only those cases of aortic stenosis which were "uncomplicated by deforming lesions of other valves," that is, aortic valvular disease without significant mitral involvement. Eighty-two per cent of the

patients had a mitral systolic murmur and slightly less than 30 per cent a mitral diastolic murmur. Considering that observation and the additional fact that this patient did not have particularly striking left auricular enlargement, I would predict that even if she did have mitral stenosis it was minimal.

DR. WOOD: In other words, if this patient did not actually have mitral stenosis the murmur was a so-called Austin-Flint murmur. Mr. Au, from a statistical standpoint, assuming that this patient does have rheumatic heart disease, is it more likely that the mitral valve would also be involved?

MR. MAN HING AU: Involvement of both the aortic and mitral valves is more common than involvement of the aortic valve alone.

DR. WOOD: Then you disagree with Mr. White.

MR. AU: I believe the patient probably had involvement of the mitral valve although it may have been minimal. According to Clawson, Bell and Hartzell,² who studied a group of 130 patients with chronic endocarditis, fifty had involvement of both the aortic and mitral valve whereas the mitral valve alone was affected in forty-four and the aortic valve alone in thirty-two.

DR. WOOD: Can you meet Mr. Au's argument, Mr. White?

MR. WHITE: I am not anxious to take issue with him. I cannot say that the mitral valve was not involved; I merely state that it does not have to be involved.

MR. STANLEY L. LONDON: When this patient was admitted for the first time, a mitral diastolic murmur was described. Following complete digitalization the murmur disappeared. Had this patient had an organic lesion of the mitral valve one would not expect the murmur to disappear completely under those circumstances. On the other hand, if the mitral stenosis was relative, that is, due to enlargement of the left ventricle after digitalization, with decrease

¹ KUMPE, C. W. and BEAN, W. B. Aortic stenosis: a study of the clinical and pathologic aspects of 107 proved cases. *Medicine*, 27: 139, 1948.

² CLAWSON, B. J., BELL, E. T. and HARTZELL, T. B. Valvular diseases of the heart with special reference to the pathogenesis of old valvular defects. *Am. J. Path.*, 2: 193, 1926.

in the size of the left ventricle, the murmur might well have disappeared.

DR. WOOD: In other words, you suggest that the murmur was not organic.

MR. STANLEY N. ROKAW: It should be pointed out that the murmur later reappeared, and I believe it is a well established clinical fact that the diastolic murmur of mitral stenosis may appear, disappear and reappear depending upon the functional state of the heart.

DR. WOOD: Your point is well taken. The murmur of mitral stenosis may change in intensity or actually disappear with a change in the heart rate, rhythm or other factors. Therefore, I think, Mr. London, that one cannot rule out an organic lesion because of the ephemeral nature of the murmur. A similar sequence may be observed with aortic diastolic murmurs although it is less common. As has been pointed out a diagnosis of mitral stenosis cannot be made dogmatically but it probably was present.

MISS ELIZABETH HAPPEL: It is of interest that in Karsner's series of 200 cases of calcific aortic disease,³ of eighteen patients with presystolic mitral murmurs, fifteen had deforming mitral stenosis at autopsy, whereas of fifteen patients who had a mid-diastolic murmur only nine had deforming mitral stenosis. The fact that this patient's murmur was mid-diastolic in time may, on the basis of Karsner's experience, lessen the likelihood of her having organic mitral stenosis.

DR. WOOD: In other words, the timing of the murmur may be of some import in deciding whether or not it is organic.

MISS HAPPEL: Yes.

DR. WOOD: What do you think about this point, Mr. Berg?

MR. LEONARD BERG: I think it sounds logical, Dr. Wood. I believe it is also worth mentioning that the absence of chronic auricular fibrillation so often associated with rheumatic mitral stenosis and the absence of the high peaked or split P waves which

are common in the electrocardiogram of patients with organic mitral valvular disease make one question the diagnosis of organic mitral stenosis.

MR. THOMAS J. WALSH, JR.: It seems to me that one must emphasize the fact that changes in the left ventricle itself may modify the character of the murmur of mitral stenosis so that none of the previously mentioned points can be applied in an all or none fashion.

DR. WOOD: It is apparent that there is a definite division of opinion about the question of mitral stenosis and since only the pathologists can settle this question I should like to go on and ask Mr. Heideman whether he thinks any other cardiac lesion need be considered.

MR. MILO L. HEIDEMAN, JR.: Late in this patient's course she developed a rather slow cardiac rate and runs of ventricular extrasystoles; I wonder whether myocardial damage and consequent interference with the conduction system may have developed because of coronary artery involvement. Digitalis may have had a role in these changes.

DR. WOOD: One must certainly consider abnormalities of the coronary circulation in view of the fact that the patient had severe aortic valvular disease; it is well known that aortic valvular disease may in its progression involve the coronary ostia. Further, a patient in this age group may have coronary sclerosis *per se*. What was the relation, if any, of coronary sclerosis to calcific aortic disease in the patients from the Cincinnati General Hospital?

MR. ROKAW: The authors specifically made the point that although coronary sclerosis occurred in a high percentage of their patients, the degree of coronary sclerosis could not be correlated with the extent of aortic valvular sclerosis. In some of their patients calcification of the aortic valve did progress to the point where the ostia of the coronary vessels were involved as you have just indicated.

MISS HAPPEL: In Karsner's series 51.5 per cent of the patients died in an episode of

³ KARSNER, H. T. and KOLETSKY, S. Calcific Disease of the Aortic Valve. Philadelphia, 1947. J. B. Lippincott Co.

congestive failure. Although twenty-three of the 200 patients died suddenly, syncope occurred in only three. These observations seem at odds with those generally held previously.

MR. LUND: I should like to mention the possibility that the patient may have had a bicuspid aortic valve.

DR. WOOD: Your suggestion is a good one. Could a bicuspid valve give rise to these signs?

MR. LUND: It certainly may be associated with both systolic and diastolic aortic murmurs.

DR. WOOD: Let us now turn to the possible thyrotoxicosis. This patient's thyroid gland was said to have been enlarged and nodular. Although the basal metabolic rate was very high, the cholesterol was never depressed. Furthermore, the results of the study of radioactive iodine excretion were not impressive on the one occasion that the test was performed. Mr. Schulz, do you believe that Dr. Moore will show us a toxic nodular goiter or will this be a nodular thyroid without evidence of activity?

MR. DALE M. SCHULZ: I believe that all of the findings can be explained on factors other than thyrotoxicosis and do not think that she had that disease. Her response to therapy was not impressive.

DR. WOOD: I think you can defend your hypothesis very well but how do you account for the high basal metabolic rate?

MR. SCHULZ: In aortic stenosis *per se* the basal metabolic rate can be quite elevated.

DR. WOOD: Can anyone comment on the relation of aortic stenosis to an elevated basal metabolic rate? Are you familiar with that subject, Mr. Levitt?

MR. JOSEPH LEVITT: Dr. Levine described this entity recently.⁴

DR. WOOD: Yes, in 1947 Levine reported four cases of aortic stenosis and in all of these the patients exhibited the clinical picture of hyperthyroidism. All four at post-mortem examination had normal thyroids.

Can anyone comment on the pathologic physiology of this syndrome? Why should the basal metabolic rate be elevated in aortic stenosis?

MR. WALSH: In that article it was postulated that the hypertrophy of the ventricle might explain the increased oxygen utilization. Levine found that in his four patients the average weight of the hearts was approximately 500 Gm. To test his hypothesis he studied another group of hearts from patients with aortic stenosis without elevated basal metabolic rates. The hearts from this second group of patients weighed on the average approximately 533 Gm. In order to make the original theory sound one would have to assume that the patients in the second series were all hypothyroid. Since this assumption is not tenable, the pathologic physiology of the syndrome remains unexplained.

DR. WOOD: You have summarized the situation well, Mr. Walsh. What explanation do you offer for the elevation of the basal metabolic rate?

MR. WALSH: Congestive heart failure elevates the basal metabolic rate.

DR. WOOD: On the other hand, the basal metabolic rate was elevated even when the patient was compensated. Will anyone defend the position that this patient indeed had hyperthyroidism?

MR. ROKAW: It seems to me, Dr. Wood, that one cannot disregard without serious consideration the combination of factors here. I should like to review them. This patient had a persistently elevated basal metabolic rate. It is true that her blood cholesterol was not low but many investigators have found that the cholesterol level does not always follow closely fluctuations in thyroid activity. The excretion of 80 per cent of the ingested radioactive iodine is likewise against a diagnosis of hyperthyroidism, but this patient had previously received iodine therapy and Means and others have found that not only can one change the metabolism of a given dose of radioactive iodine but also one can increase the serum protein-bound iodine in such patients merely

⁴ SMITH, J. A. and LEVINE, S. A. Aortic stenosis with elevated metabolic rate simulating hyperthyroidism. *Arch. Int. Med.*, 80: 265, 1947.

by giving Priodax for a cholecystogram. This tracer dose was given within three weeks of the termination of therapy with Lugol's solution; this fact may have accounted for the relatively high excretion of radioactive iodine. The patient had lost 15 pounds during the course of her illness and she had the fine skin of the thyrotoxic patient. No eye signs were described. Although it is stated in the protocol that she did not sweat excessively, some of the people who saw her on the ward report that on occasion she sweated profusely. Her very rapid pulse rate could have been explained on the basis of cardiac decompensation. Finally she had definite enlargement of the thyroid gland. One cannot state with much assurance whether the thyroid gland was hyperactive or not.

DR. WOOD: Although there was definite doubt on the part of the staff as to whether this patient did have hyperthyroidism she was treated as though she did. Mr. London, if you had been the medical house officer in charge of this patient, would you have done differently?

MR. LONDON: I think I would have treated her essentially the same way. One could not rule out thyrotoxicosis and since part of the clinical picture of congestive failure may have been due to hyperthyroidism, one certainly was justified in treating the patient in the manner described. I actually do not believe that she had thyrotoxicosis.

DR. WOOD: Mr. Levitt, what would you say about treating a patient with chronic cardiac failure for hyperthyroidism even though she were apparently euthyroid?

MR. LEVITT: It has been shown that digitalis will exert a greater effect in patients with thyrotoxic heart disease if the thyrotoxicosis is controlled first. If I suspected that the patient were the least bit hyperthyroid, I would attack that aspect of the problem first.

MR. ROKAW: Some years ago thyroidectomy was performed on patients with severe cardiac failure whether they had thyrotoxicosis or not.

DR. WOOD: Dr. Blumgart⁵ was one of the first advocates of that procedure and at the recent meetings of the Association of American Physicians Dr. Blumgart⁶ again reported on the use of I¹³¹ in the treatment of chronic congestive heart failure. On the basis of that work it would seem reasonable to have treated this patient with radioactive iodine whether or not she was hyperthyroid. Actually there was little response to therapy as evidenced by determinations of the basal metabolic rate. As with the problem of mitral stenosis we cannot say with confidence whether this patient's thyroid gland was hyperactive or not. Conceivably the signs of hyperthyroidism may have been due to aortic stenosis *per se*.

MR. LEVITT: In a patient whose nodular goiter increases in size under observation one cannot rule out carcinoma completely.

DR. WOOD: That diagnosis would have to be considered. Do you think it is likely?

MR. LEVITT: Not likely but there is a possibility.

DR. WOOD: Recently at a meeting of the Washington University Medical Society we were reminded that a significant number of patients with thyroid nodules develop "carcinomatous degeneration." Perhaps Dr. Robert Moore will show us a malignant change here.

MR. ROKAW: May we ask Dr. Grunow if the pulmonary lesion conceivably could have represented a metastasis?

DR. OTTO H. W. GRUNOW: The pulmonary findings from the radiologic point of view were much more in keeping with either pneumonia or pulmonary infarction.

DR. WOOD: Dr. Heideman, what two pulmonary lesions would you consider primarily?

⁵ BLUMGART, H. L., LEVINE, S. A. and BERLIN, D. D. Congestive heart failure and angina pectoris, therapeutic effect of thyroidectomy on patients without clinical or pathologic evidence of thyroid toxicity. *Arch. Int. Med.*, 51: 866, 1933.

⁶ BLUMGART, H. L., FREEDBERG, A. S., KURLAND, J. and URELES, A. L. Treatment of intractable angina pectoris and congestive failure in euthyroid patients by producing hypothyroidism with I¹³¹. *Tr. A. Am. Physicians*, to be published.

MR. HEIDEMAN: Bacterial pneumonia and pulmonary infarction.

DR. WOOD: Yes, pulmonary infarction is common in congestive heart failure and so is bacterial pneumonia. Which do you believe was present here, Mr. Heideman?

MR. HEIDEMAN: I believe the fact that the patient developed fever, leukocytosis and a left shift in the differential at the time when the pulmonary findings increased suggests pneumonia rather than pulmonary infarction.

DR. WOOD: On the other hand, jaundice makes one think of pulmonary infarction.

MR. HEIDEMAN: I do not see why the direct bilirubin would be elevated in that case.

DR. WOOD: No, that particular result is not explicable on the basis of a diagnosis of pulmonary infarction.

MR. LONDON: The patient's liver function may have been deranged because of chronic congestive failure and development of cardiac cirrhosis.

DR. WOOD: Let us now consider the problem of this patient's psychosis. It was a very serious complication of her illness and suggests several explanations.

MR. WHITE: Conceivably, the psychosis may have been associated with aortic stenosis. In 5 to 10 per cent of patients with aortic stenosis there is accompanying mental aberration which cannot always be correlated with pathologic findings in the brain. Second, patients who have had cerebral thromboses may have subsequent degeneration of cerebral tissue and become psychotic. Finally this patient may have had a so-called "cardiac psychosis," which not uncommonly develops in patients with cardiac failure as they are becoming compensated.

DR. WOOD: Mrs. McChesney, which diagnosis do you favor?

MRS. MARGARET B. MCCHESENEY: I remember seeing this patient on the ward. The psychosis was quite striking and most of us who saw her believed that the clinical picture was representative of cardiac psychosis. As has been pointed out cardiac psychoses often develop as the patient's

cardiac failure improves, and that situation obtained here.

DR. WOOD: Cardiac psychosis must certainly be seriously considered. As Mr. White suggested, however, aortic stenosis also looms as an important possibility on the basis of the findings in Kumpe and Bean's series. Some of these patients develop psychoses because of cerebral anoxia due to the obstruction of cardiac output by the stenotic valve; in others there may be vascular disease of the brain. Will Dr. Moore show us any pathologic lesion in the brain?

MRS. MCCHESENEY: In true cardiac psychosis I doubt that pathologic findings are demonstrable. I should like to mention one other possibility, however. This patient may have had carcinoma of the thyroid with metastatic cerebral lesions.

DR. WOOD: Yes, that is a possibility. In summary, it seems to me that most of us agree that this patient had rheumatic heart disease which involved the aortic valve. As so often happens the patient did well until she reached her sixth decade. Then her cardiac function became seriously impaired and the patient developed symptoms of congestive heart failure. Whether or not she had mitral stenosis remains a question for the pathologists to settle. Statistically she should have it but it is conceivable that the mitral diastolic murmur described was of the so-called Austin-Flint type. Whether the nodular goiter which was palpable was toxic cannot be stated; the manifestations of thyrotoxicosis could have been due to aortic stenosis. The pulmonary lesions may have been either bronchopneumonia complicating pulmonary infarction or congestive heart failure. Again, we are unable to state which one was responsible although I believe we lean toward bronchopneumonia. There are two good explanations for the psychosis and it remains to be determined whether Dr. Moore will demonstrate encephalomalacia. Are there any other possibilities?

MR. BERG: It has recently been pointed out that patients with rheumatic heart

disease may at autopsy exhibit lesions of the cerebral vessels which resemble the lesions in rheumatic carditis and which may or may not cause symptoms. Such lesions could have been responsible for this patient's psychosis.

DR. WOOD: Are you referring to rheumatic encephalitis?

MR. BERG: The process is not primarily encephalitic but rather vascular in nature with secondary encephalomalacia. Whether or not it represents a definite rheumatic lesion is doubtful.

Clinical Diagnoses: Rheumatic heart disease with aortic stenosis, aortic insufficiency and ? mitral stenosis; congestive heart failure and chronic passive congestion; nodular goiter, ? toxic; bronchopneumonia, ? pulmonary infarction.

PATHOLOGIC DISCUSSION

DR. F. BERTOLI: At autopsy there was distinct pallor of the skin and mucous membranes and marked persistent pitting edema of the lower extremities.

The thyroid gland weighed 40 Gm. The left lobe was small and contained prominent follicles. Almost entirely replacing the right lobe was a smooth, ovoid, encapsulated nodule 3 cm. in average diameter. The peripheral areas were yellow gray, hard and surrounded by a fibrous capsule 1 or 2 mm. in thickness.

The heart was markedly enlarged, weighing 710 Gm. There was a small amount of fluid in the pericardial cavity and focal areas of fibrous thickening of the pericardium. Hypertrophy of the myocardium, especially of the left ventricle and left atrium, was prominent. The aortic orifice was markedly narrowed by two partially fused coronary cusps with an incomplete raphe; the posterior cusp was wider than normal. The cusps were thickened by small yellow gray, irregular, brittle nodules. A round defect, $\frac{1}{2}$ cm. in diameter, with smooth rounded edges was present in the posterior cusp. At the apex in the left ventricle there was an oval, gray, firm mass 1.5 by 1 by 0.5 cm. in its dimensions. Its surface



FIG. 1. The aortic valve with calcified masses on the coronary cusps and a circular defect in the posterior cusp. Note the absence of arteriosclerosis in the aorta.

was trabeculated and it was firmly attached to the endocardium which was markedly thickened, white and smooth in the adjacent area. Beneath this thrombus the myocardium was thin with a fibrous scar extending through the septum and the right ventricular wall. Attached to the scar in the right ventricle there was a similar but smaller thrombus.

The lungs were of increased weight. A few fibrous pleural adhesions were present and in the lower lobe of the right lung there were numerous bulging, wedge-shaped, dark red, elevated, dry, well defined foci measuring 1 to 4 cm. in diameter; there was a finely granular deposit on the overlying pleura. About these infarcts were foci of firm, gray, granular bronchopneumonia. The remaining portions of the lungs were brown red, smooth, normally crepitant and exuded a moderate amount of thin frothy fluid on pressure. In the lumina of the secondary and tertiary branches of the pulmonary artery leading to the right lower lobe there were several dark red, friable thrombi.

Except for an infarct in the upper pole of the spleen and congestive changes in the liver and spleen, the other viscera including the brain were not grossly remarkable.

DR. ROBERT A. MOORE: The first photograph (Fig. 1) is of the heart. There were calcified masses within the substance of the

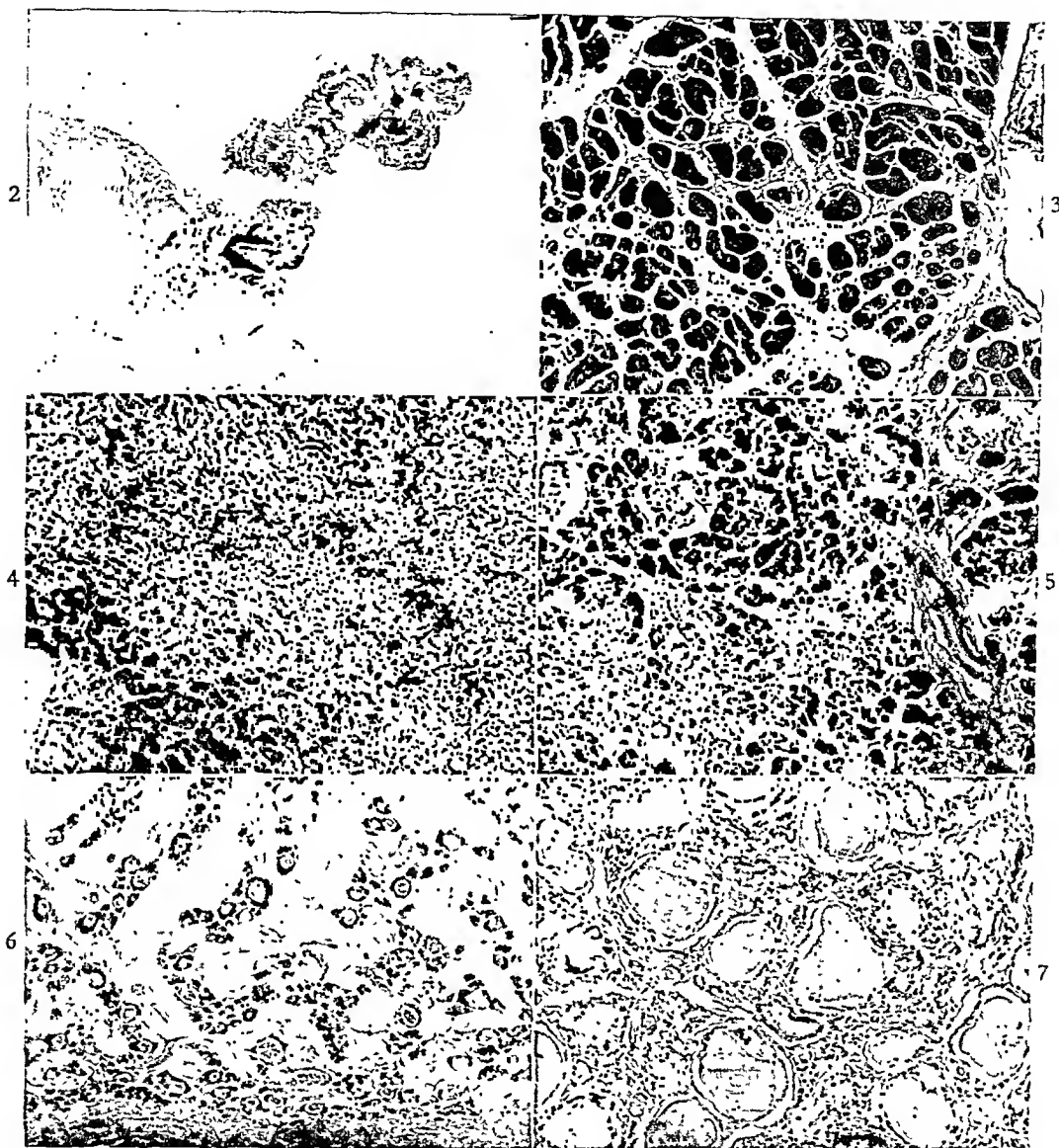


FIG. 2. Total section through the base of the left ventricle and the deformed, calcified cusp of the aortic valve.

FIG. 3. Diffuse interstitial fibrosis in the myocardium.

FIG. 4. Central atrophy of the hepatic cells with increased fibrous tissue about the central veins and adjacent sinusoids.

FIG. 5. Interstitial fibrosis and separation of the acini in the pancreas with a resulting lobulated appearance typical of chronic passive congestion.

FIG. 6. Microfollicles and degenerated stroma at the edge of the adenomatous nodule in the thyroid.

FIG. 7. Interstitial fibrosis in the thyroid. Note the absence of hyperplastic changes in the epithelium of the acini.

aortic valve, more in the right anterior cusp than in the others and a defect in the posterior cusp measuring 5 by 6 mm. in diameter. The absence of arteriosclerosis in the aorta was worthy of note. Figure 2 is a section of the base of the left ventricle and the aortic lesion; it is apparent that the disease is entirely healed, whatever it may

have been. There is nothing but fibrous tissue and large masses of calcium throughout the valve and in the valve ring. In Figure 3 a section of the myocardium is seen in which there is slight fibrosis throughout the interstitial tissue. The next photograph (Fig. 4) is of a section of the liver in which the hepatic cells of the central portions of

the lobules have atrophied and been replaced by an increased amount of connective tissue about the central vein and sinusoids. This finding indicates that the patient had chronic passive congestion of the liver for some period of time with consequent development of congestive cirrhosis. Figure 5 is a section from the pancreas in which there is interstitial fibrosis and accentuation of the lobular character, changes which again are a manifestation of chronic passive congestion of long-standing.

In Figure 6 is a portion of the nodule in the right lobe of the thyroid in which there were numerous small acini, containing in some areas a small amount of colloid embedded in acellular, homogeneous material, changes typical of degeneration of a thyroid adenoma. The remainder of the thyroid (Fig. 7) is not involved by the adenomatous process; the acini are of variable size, filled with rather dense homogeneous colloid. The epithelial cells are of a cuboidal or even flattened character. In between the acini there is considerable increase in the fibrous connective tissue. The last photograph (Fig. 8) is of a section from the lung taken from an area adjacent to an infarct; fluid and a few cells are present in all the alveoli. Cultures of this part of the lung revealed no growth and stains for bacteria show none in these sections. Whatever organisms produced the pneumonia had therefore been destroyed by the time the patient died.

Review of these pathologic findings enables certain interpretations, which are relative to many of the questions raised during the clinical discussion, to be made. First, the cusps of the aortic valve were deformed and unequal but did not resemble a typical bicuspid valve of the congenital type although they did produce both aortic stenosis and insufficiency. The insufficiency was probably on the basis of the defect of the posterior cusp which was of considerable magnitude. There was no disease of the mitral valve, but there was arteriolar disease and that had led to the loss of myocardial tissue and interstitial fibrosis throughout.

The question of whether or not the pa-

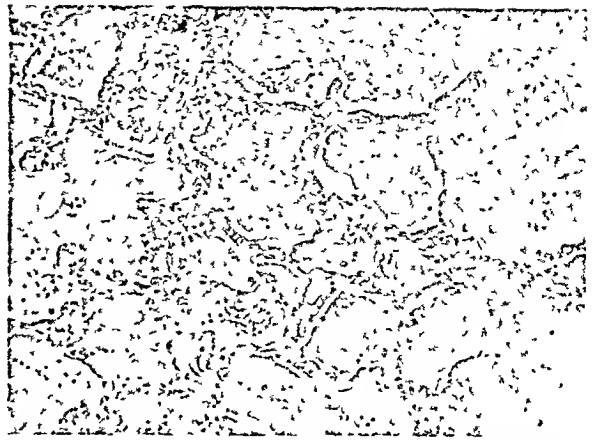


FIG. 8. Edema fluid and slight cellular exudate in the alveoli of the lung indicative of both edema and bronchopneumonia.

tient had thyrotoxicosis certainly cannot be answered definitively on the basis of histologic examination. However, one is justified in stating that there is less than a 50 per cent chance that this thyroid was toxic. The latter statement is based on the fact that in most instances toxicity of the thyroid is associated with hypertrophy and hyperplasia of the epithelial cells although not invariably so. There are other reasons against this gland having been hyperactive in the recent past. For example, the remainder of thyroid tissue other than the adenoma represents a so-called "burnt out" thyroid such as might result from hyperthyroidism at an earlier date. Second, one might have expected to find cirrhosis of the liver of some magnitude. Such was not the case. Cirrhosis is found in association with a significant number of cases of hyperthyroidism. It is probable that some of the interstitial fibrosis in this gland resulted from the radiation used in therapy.

There were infarcts and bronchopneumonia in the lower lobe of the right lung which undoubtedly contributed to the terminal clinical episodes. There is no anatomic explanation of the psychosis; the brain was both grossly and microscopically normal to ordinary examination and probably would be to special examination as there are no significantly constant morphologic changes in the brain in psychoses of this type.

If one rigidly applies the usual criteria

for identification of rheumatic endocarditis and arteriosclerosis of the aortic valve, he finds it necessary to postulate both diseases were present here because both the substance and the base of the cusps are involved. Personally, I would prefer to accept this case as probably rheumatic in origin but with the same reservations as were expressed clinically. Despite the absence of a definite history of rheumatic fever it is quite likely that this lesion was rheumatic. The absence of arteriosclerosis in the aorta would, I think, be against a diagnosis of the Mönckeberg type of calcific aortic stenosis.

DR. WOOD: The location and superficial appearance of the large lesions on the aortic valves remind one of the vegetations of bacterial endocarditis. Dr. Moore, do you consider it possible they might represent healed, calcified vegetations?

DR. MOORE: I was not going to bring that up because I have no definitive proof for my own belief that all cases of calcific aortic stenosis represent healed bacterial endocarditis. There is excellent authoritative opinion that rheumatic endocarditis alone can result in this type of calcification and distortion of the valve. The usual

rheumatic valvulitis, however, does not result in such destruction and calcification in the affected tissue, so I believe there must be some additional factor responsible for that type of reaction which is not present in ordinary cases of that disease. Since both destruction of the valve and calcified masses in older vegetations are recognized features of proven bacterial endocarditis, the postulate that the disease is the underlying process in the development of calcific aortic stenosis appears reasonable.

Anatomic Diagnoses: Chronic endocarditis of the aortic valve with nodular calcification of the coronary cusps and defect in the posterior cusp; healed infarct of the left ventricle and intraventricular septum at the apex of the heart; focal fibrosis of the myocardium; partially organized thrombi in the apices of the right and left ventricles; passive congestion of the lungs, liver, spleen and pancreas with fibrosis of the liver; partially depigmented and recent infarcts of the lower lobes of the right lung with bronchopneumonia; solitary adenomatous nodule in the right lobe of the thyroid; fibrosis of the thyroid without evidence of hyperplasia.

Special Feature

The Southern Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE THIRD ANNUAL MEETING, NEW ORLEANS,
JANUARY 29, 1949

PROCEEDINGS

(Read by Presentation)

OBSERVATIONS ON TWO NEWER HEMOPOIETIC VITAMINS—VITAMIN B₁₂ AND ANIMAL PROTEIN FACTOR. *William J. Darby, M.D. and (by invitation) Edgar Jones, M.D.* From The Departments of Medicine and Biochemistry, Vanderbilt University School of Medicine, Nashville, Tenn.

Patients with anemias associated with megaloblastic arrest respond hemopoietically to four types of nutritional factors or metabolic products: the pteroylglutamates, vitamin B₁₂, microbial animal protein factor (APF) and thymine. Three of these are available in crystalline form; the fourth (APF) is not but may be quantitated by chick growth studies.

We have made observations on the responses to crystalline B₁₂ (administered parenterally) in eleven patients with pernicious anemia, nutritional macrocytic anemia or sprue. These studies have included evaluations of the minimal effective dosage for induction of hemopoietic and clinical remissions and for maintenance of the patient. These observations to date indicate the approximate equivalence of 1 microgram of crystalline B₁₂ to 1 USP unit of antipernicious anemia liver extract.

In pernicious anemia the remissions produced by B₁₂ therapy have been characterized by relief of glossitis, an increased sense of well being, initial hemopoietic response typical of an adequately treated anemia patient, maturation of the megaloblastic marrow, weight gain, decrease in fecal urobilinogen and, in two patients, disappearance of early neurologic symptoms. In two cases of sprue the results have been less clearly defined and our experience indicates a greater quantitative requirement in this syndrome. Nutritional macrocytic anemia has responded in a manner comparable to pernicious anemia. Evidence will be presented indicating an approximate correspondence of

activity of APF in pernicious anemia (parenteral administration) and in the chick.

Since these two factors are effective parenterally it does not appear that they correspond to Castle's extrinsic factor although their association with animal protein would imply that they may.

CLINICAL AND LABORATORY RESIDUALS IN PATIENTS TREATED FOR SPRUE. *Herbert J. Fox, M.D. (Introduced by Eugene A. Stead, Jr., M.D.)* From Duke University School of Medicine, Durham, N. C.

A follow-up clinical and laboratory study was made on twenty patients previously diagnosed as having sprue who had had from five to fourteen years of nutritional rehabilitation and specific therapy. Each had had a chronic illness characterized by loss of weight, anemia, glossitis, diarrhea, meteorism and steatorrhea.

This study was undertaken to determine the residual disability and laboratory evidence of absorptive defects in sprue that persisted despite prolonged therapy. Nine of the twenty patients had not achieved full rehabilitation, had remained underweight, deficient in strength and had periodic recurrences of diarrhea and glossitis. Physical activity was restricted. Dietary fat was tolerated poorly. Continued liver therapy was necessary. A five-day fat balance test showed a sub-normal absorption of dietary fat in all nine patients. Their stools, by a measured fecal output over three-day periods, were increased in bulk. Mild anemia with a tendency toward macrocytosis was present. Unemulsified vitamin A showed flat absorption curves in contrast to normal curves with emulsified material. Roentgenologic study of the small intestine showed coarse irregularities and segmentation alternating with dilatation. The effect of folic acid on fat absorption was observed in seven of these nine patients. Although they had received maintenance doses of folic acid, 15 to 30 mg. daily for six months or longer and had

bowel habit improvements not seen in liver therapy, still all seven showed steatorrhea.

Eleven of the twenty had not received specific therapy for several years and were apparently fully recovered, showing none of the clinical or laboratory residuals seen in the other nine patients.

The sprue syndrome apparently represents a temporary motor and absorptive abnormality of the intestines from nutritional deficiency, or a more permanent disease which persists in spite of nutritional rehabilitation and therapy. The latter may be congenital or represent a sequela of inflammatory or other damage to the gut wall.

CHANGES IN ELECTROPHORETIC PATTERNS OF SERA IN PATIENTS WITH MULTIPLE MYELOMA TREATED WITH URETHANE. *Edith S. Dillon, M.D. (by invitation), M. L. Dillon, M.D. (by invitation) and R. W. Rundles, M.D.* From Duke University School of Medicine, Durham, N. C.

In six patients with multiple myeloma treated with urethane, fever and bone pain at rest and during activity subsided and anemia, hyperglobulinemia and proteinuria were ameliorated or corrected. Abnormal plasma cells in the bone marrow became altered in appearance and decreased in number or disappeared from the marrow. After six to eight months there was x-ray evidence of recalcification of bone.

Electrophoretic studies on sera of four of these patients showed conspicuous reduction in the amount of abnormal serum globulin after urethane therapy. In one patient globulin with gamma mobility comprised 45.7 per cent of the total serum protein before treatment. A total dosage of 240 Gm. of urethane was given orally over a period of two months. Five months after completion of therapy the gamma globulin component was 23.8 per cent and at nine months it was 22.9 per cent. In a second patient with 49 per cent gamma globulin before treatment there was a fall to 18 per cent in four months and 19.1 per cent at seven months. In a third patient "M" globulin comprised 45.2 per cent of the serum protein before treatment and 33.4 per cent three and one-half months later. The abnormal globulin rose again to 40.6 per cent accompanied by a decline in hemoglobin, red count and hematocrit and the reappearance of over 20 Gm. per day of Bence-Jones protein

in the urine. A fourth patient excreting about 25 Gm. of Bence-Jones protein daily in the urine had a normal percentage distribution of serum protein components before therapy. After two months of urethane the gamma globulin fell from 10.5 per cent to 8.5 per cent with a 75 per cent reduction in the amount of Bence-Jones protein in the urine.

ACTIVATION OF SERUM PROTEOLYTIC ENZYME. *Jessica H. Lewis, M.D. (by invitation) and John H. Ferguson, M.D.* From The Department of Physiology, University of North Carolina, Chapel Hill, N. C.

Normal blood contains a powerful proteolytic enzyme system which, if fully activated, is capable of destroying all the fibrinogen and probably much of the other plasma protein in a few minutes. Serum contains enzyme precursor (proenzyme) and enzyme inhibitor (anti-enzyme). *In vivo* activation occurs only under certain rare pathologic conditions.

We have set up systems for study of the activation of this proenzyme *in vitro*, using various "activators" including chloroform, streptokinase and staphylokinase. Proteolytic activity is measured by the rate of lysis of a standard fibrin clot.

Proenzyme is prepared from (1) human, (2) canine (3) bovine serum by 25 per cent alcohol fractionation at 0°C. This fraction contains almost all the proenzyme and a reduced amount of anti-enzyme. Spontaneous activation of these preparations did not occur.

Chloroform treatment of the proenzyme preparations causes further marked reduction of the antifibrinolytic activity of these fractions. Fibrinolytic activity appears in these preparations only slowly and rarely to maximal amounts. It is concluded that the main action of chloroform is to remove enzyme inhibitors and to allow either spontaneous activation or activation by substances already present in the serum fractions. Streptokinase readily activates human proenzyme but does not affect dog or bovine preparations. In optimal amounts its effect is immediate but in suboptimal amounts a period of preliminary incubation with proenzyme is necessary for maximal fibrinolytic activity. Staphylokinase activates both human and dog proenzyme but does not affect bovine material. The kinetics of the staphylokinase reaction also

differ from streptokinase in that even in optimal amounts staphylokinase reacts relatively slowly, the rate being dependent upon the temperature. Streptokinase and staphylokinase are relatively heat stable, as is the proenzyme, while the activated enzyme is markedly heat labile.

In conclusion, the applicability of these facts to the measurement of human and dog proenzyme is presented.

THERAPEUTIC USE OF RADIOACTIVE GOLD IN MALIGNANT DISEASE. *P. F. Hahn, M.D.*
From The Cancer Research Laboratories,
Meharry Medical College, Nashville,
Tenn.

Radioactive gold¹⁹⁸ is produced by a neutron-gamma reaction in the chain reacting pile from the 100 per cent naturally occurring gold.¹⁹⁷ Therefore, there are no undesirable side reactions or contaminant isotopes produced. Gold¹⁹⁸ lends itself readily, when in the colloidal state, to administration by vein in the treatment of diseases of the lymphoid-macrophage system. It is also useful in the treatment of discrete tumor masses by direct infiltration as the colloid. The half-life (2.7 days) is sufficiently long for the isotope to perform its required work, i.e., delivering radiation over an integrated period of slightly over a week rather than in a short burst. Its life is not so long but that one is able to "titrate" the ionizing radiation in the patient and certainly not long enough to act as a carcinogenic agent in itself. Its biologic behavior is comparatively well understood and, as the colloid of the metallic element, is not susceptible to solution by tissue fluids. The chemical behavior of the element is well known. To date it has been found that once this material is delivered underneath the skin the tissue tolerance for radiation is several times what was anticipated. It is non-toxic. Its administration does not give rise to radiation sickness. The cross section to thermal neutrons ranges from 100 to 200 times that of most isotopes. The degree of dispersal of the gold colloid is very high, the particle size being of the order of magnitude of 60 milli-micra, there being approximately 3 trillion particles per cc. of colloid suspension. Each of these acts as a near-point beta emitter. The mean free path of the beta particle in the tissue is of the order of 3.8 mm. Thus adjacent structures and tissues are relatively unaffected in contrast to the radiation produced by use of radium needles and

radon seeds. Thus with gold colloid the beta radiation is used to its fullest extent and the gamma is relatively negligible, constituting approximately 10 per cent of the total ionization response obtained.

The chief obstacle to widespread use of this material in the treatment of malignant tumors at the present time is lack of knowledge of the beta ray tolerance of various tissues. It is also difficult on many occasions to estimate the volume of tissue subjected to infiltration and therefore we are occasionally unable properly to estimate the equivalent roentgen dosage delivered to such tissues. Radio-autography is being employed in an attempt to study the degree to which this material is diffused in the tissue infiltrated. Also certain spreading agents are being investigated as to their capacities to modify such diffuse localization of the isotope. This isotope promises to be very useful in the future treatment of neoplasms.

TREATMENT OF VARIOUS INFECTIONS WITH PROCAINE PENICILLIN IN OIL WITH 2 PER CENT ALUMINUM MONOSTEARATE. *Harold L. Hirsh, M.D. and Walter Kurland, M.D.*
(Introduced by *Hugh S. Hussey, M.D.*). From The Georgetown University Medical Division, Gallinger Municipal Hospital and the Department of Medicine, Georgetown University School of Medicine, Washington, D. C.

Adequate preparations of procaine penicillin in oil with 2 per cent w/v aluminum monostearate give therapeutically effective blood concentrations for at least ninety-six hours and generally for one hundred twenty hours. Significant blood concentrations have been found within one hour after injection.

Our previous experience has demonstrated that penicillin therapy for about five days is generally sufficient in the treatment of any acute infection. The present study was undertaken for the purpose of determining whether infections caused by organisms such as the pneumococcus and streptococcus could be adequately treated by a single 1 cc. dose of procaine penicillin in oil with 2 per cent w/v aluminum monostearate containing 300,000 units of procaine penicillin.

Twenty-five patients with scarlet fever are included in this series. A prompt response was noted in all patients. The duration of fever after therapy was started averaged thirty-eight hours.

Streptococci disappeared within forty-eight hours from the throats of all patients from whom positive cultures were obtained before therapy was started. One patient had a recurrence of the hemolytic streptococcus on the fourth day which persisted until another injection of procaine penicillin in oil with aluminum monostearate was given on the eleventh day. Another patient developed purulent otitis media on the tenth day which responded to therapy with aqueous penicillin. Still another patient developed serous meningitis on the seventh day and a fourth, evidence suggestive of acute rheumatic fever on the eleventh day.

Sixteen patients with lobar pneumonia diagnosed on the basis of history and physical findings, serial roentgenograms and/or laboratory studies have been treated with a single injection of the preparation. In all patients the response was prompt and the temperature fell below 100°C. within twenty-four hours. Convalescence was uneventful in all patients.

One patient with streptococcal pharyngitis was treated in an identical manner and made an uneventful recovery.

Three patients with cellulitis were given two injections (300,000 units each) at five-day intervals with complete resolution of the involved area.

The results in this series of patients are comparable to those seen in patients treated with other established penicillin regimens.

EFFECT OF DIHYDROERGOCORNINE ON THE PULMONARY RESPONSE TO HISTAMINE AND METHACHOLINE IN SUBJECTS WITH BRONCHIAL ASTHMA. *John F. Curry, M.D., Job E. Fuchs, M.D. and Samuel E. Leard, M.D. (Introduced by Harold Jeghers, M.D.)* From The Robert Dawson Evans Memorial, Massachusetts Memorial Hospital and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

It has been reported that interruption of the sympathetic nervous system in the lung brings about cessation of asthmatic attacks in certain individuals. Presumably the operation is effective because it prevents noxious stimuli arising within the lung structure from ascending to the cranial centers and producing reflex bronchoconstriction. In a few subjects with bronchial

asthma we have been able to demonstrate that procaine block of the sympathetic pathways of the lung reduces the pulmonary response to injected histamine and methacholine. This is of great interest in view of recently reported studies on the relationship between the degree of asthma and the pulmonary response to these drugs.

In the present communication the effect of a new sympatholytic agent, dihydroergocornine, on the pulmonary response to histamine and methacholine is reported. The method of study has been outlined in detail in previous reports. In brief, an evanescent asthma-like attack is induced by histamine or methacholine and the subsequent reduction in vital capacity and maximum ventilation is measured. Dihydroergocornine is then administered and the injection of histamine or methacholine repeated. The degree of protection is thus easily ascertained by objective measurement. The results indicate that in some cases the sympatholytic agent furnishes remarkable protection against the pulmonary reaction to histamine and methacholine. These studies present interesting clinical implications and in addition may furnish further understanding of the fundamental pathologic physiology of the lung in bronchial asthma.

STUDY OF COMPLETE PARENTERAL ALIMENTATION IN DOGS. *H. C. Meng, M.D. (Introduced by William J. Darby, M.D.)* From The Department of Physiology, Vanderbilt University School of Medicine, Nashville, Tenn.

Previous work has led to the development of a stable, fine fat emulsion which was used in an attempt to supply all necessary nutrients to dogs intravenously. The animals were apparently in good health after ten weeks of injections. However, they did show intermittent hematuria and some anemia. It was thought that the hematuria and anemia might have been due to the mechanical difficulties in voiding. The present study was undertaken in an attempt to avoid the previous difficulties and demonstrate the possibility of keeping animals completely healthy by complete parenteral feeding.

In the control period two adult male dogs were fed a complete basal diet which furnished 80 calories per Kg. of body weight per day of which 50 per cent came from carbohydrate,

16 per cent from protein and 34 per cent from fat. Immediately following this period they were given a diet containing the same amount of carbohydrate, protein and fat, but it was infused exclusively by vein. Water was allowed by mouth *ad libitum*, and liver extract and folic acid were given intramuscularly every week. Protein was furnished in the form of the casein hydrolysate, amigen. The fat emulsion contained 10 per cent olive oil which was stabilized with 0.5 per cent span 20, 0.4 per cent asolectin and 0.1 per cent sodium cholate. It was homogenized in a high pressure viscolizer. Vitamins A, D and E were incorporated in the emulsion. The dogs were infused daily for four weeks and then sacrificed.

There was never any hematuria or anemia and the animals remained healthy, lively and in good spirits throughout. Extensive laboratory tests were performed during the experimental period, and the outstanding feature of all of them was their constancy. The nitrogen balance was negative during the first week but was subsequently positive. There was a slight gain in body weight. Histopathologic study of the organs of the animals showed them to be entirely normal. It is concluded that this fat emulsion is non-toxic and that the body is capable of utilizing fat in this form.

GASTROMETRIC STUDIES BEFORE AND AFTER VAGOTOMY. *E. J. Linberg, M.D. (by invitation), K. S. Grimson, M.D. and (by invitation) J. R. Chittum, M.D.* From The Department of Surgery, Duke University School of Medicine, Durham, N. C.

Gastrometric examinations of the fasting stomach have been made before vagotomy in thirty-eight patients with peptic ulcer and at intervals afterward in fifty-six. Eleven were studied twenty-four to thirty-seven months after operation. The usual method employed intragastric balloons inflated at intervals of five to fifteen minutes using increments of 50 cc. of air to a total volume of 300 cc. Intragastric pressure was recorded continuously using a bromoform manometer. Resting intragastric pressure as judged by the tone base line was moderately increased after vagotomy. Strong fluctuations of intragastric pressure above this tone base line ceased or were markedly reduced. Stretch reflexes occasionally occurring during inflation of the balloon before vagotomy were not ob-

served afterward. Tonus contractions occurred occasionally before and after operation. Effects persisted, there being no evidence of recovery during periods of observation as long as three years.

Effects of overdistention of the stomach were studied. Three patients were tested before vagotomy and one or two weeks afterward by increasing the balloon volume to 1,000 cc. Resting tone increased with greater distention before and after vagotomy, the increase afterward being greater. Increase of contraction waves with higher volumes did not occur in patients tested during the first several weeks after vagotomy. Fifteen patients were tested twelve to thirty-eight months after vagotomy using volumes up to 1,000 cc. Increased height of the tone base line occurred, that at 1,000 cc. being double that at 300. Some patients had low contraction waves at a 300 cc. volume. These increased in height with greater distention.

Comparison of gastrometric records of motility with standard insulin tests reveals changes of motility to be more consistent, a normal pattern appearing after operation only in one patient definitely known to have an incomplete vagotomy.

MECHANISM OF REMOVAL OF SULFONATED DYES FROM BLOOD PLASMA BY MAMMALIAN LIVER. *Ralph W. Brauer, M.D. (Introduced by John Adriani, M.D.)* From The Department of Pharmacology and Experimental Therapeutics, Louisiana State University School of Medicine, New Orleans, La.

It will be shown that three factors are involved in the excretion of sulfonated phthalein dyes, especially sodium phenoltetrabromophthalein sulfonate by the liver: circulation of blood through the liver, uptake of the dye from the blood plasma by the hepatic parenchyma and re-excretion of the dye store in the hepatic cells in the bile. Data will be presented in particular with regard to the second mechanism which has been investigated by means of liver perfusion studies as well as by *in vitro* studies of liver slices. The uptake mechanism appears to be independent of metabolic processes which can be poisoned by either cyanide, fluoride or mercuric ion, and it does not appear to be interfered with by administration of India ink or of carbon tetrachloride prior to the experiment under condi-

tions which lead to a marked decrease of the BSP clearance in the intact animal. The evidence to be presented supports the concept of the liver functioning as a multiple unit extraction system in which successive units function at decreasing BSP concentrations. This concept is derived in part from the much greater efficiency of the perfused liver compared to incubated liver slices in removing BSP from the solutions with which they are brought in contact. The tendency of BSP to form little dissociated complexes with various proteins is proposed as the basis of the driving force governing the flow of dye from plasma or perfusion solutions into the liver cells. Data to be presented with regard to the other two factors just mentioned will include studies of the relative concentrations of BSP in blood plasma and liver lymph of normal and carbon tetrachloride-poisoned or India ink-injected dogs as well as preliminary data obtained by the use of BSP containing radioactive sulfur in the sulfonic acid radical of the molecule.

THERMAL SEPARATION OF RADIOMERCURY FROM RADIOSODIUM. *P. B. Reaser, M.D. (by invitation), G. E. Burch, M.D. and (by invitation) S. A. Threefoot, M.D. and C. T. Ray, M.D.* From The Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana, New Orleans, La.

A number of physiologic phenomena can be studied best by the simultaneous administration of two or more radioactive isotopes. This report is concerned with the description of a method which is practical in separating radioactive mercury from radioactive sodium (Na^{22}) and presumably from other elements with similar thermodynamic constants. Its organic combinations are characterized by instability. If they are decomposed, the consequent behavior of the Hg can be used to advantage.

To study the pharmacodynamics of diureses produced by a mercurial diuretic it is desirable to use such a compound synthesized with radio-mercury ($\text{Hg}^{203-205}$). This isotope of mercury has a physical half-life of 51.5 days. Its "practical" half-life was found to vary considerably, depending on environmental and chemical conditions.

Thirty samples of radioactive mercurhydrin and radioactive sodium (Na^{22}) were allowed to dry at room temperature. Thirty samples of a solution of radioactive sodium (Na^{22}) chloride

were prepared, to which, after drying, were added known amounts of radioactive mercurhydrin solution. After being counted all preparations were heated in an oven to 250°C . for one hour and twenty minutes. Upon removal and cooling they were again counted.

A mean of more than 99 per cent of the mercury of a mercurhydrin preparation was driven off by heat, whereas under identical conditions a sodium preparation did not change significantly. Naturally, stable mercurial salts or compounds would have to be rendered labile to heat to take advantage of vapor tension and boiling point differences.

SPECTROPHOTOMETRIC DETERMINATION OF BLOOD OXYGEN. *J. B. Hickam, M.D. and K. R. Frayser, M.D. (Introduced by Eugene A. Stead, Jr., M.D.)* From The Department of Medicine, Duke University School of Medicine, Durham, N. C.

Determination of blood oxygen content by gasometric methods is time-consuming, thus limiting the number of observations made in a single study. In many cases it is the arteriovenous difference across lung, liver, kidney or brain which is particularly desired. The present abstract reports the development of a rapid, accurate spectrophotometric method for determining the difference in oxygen content between two samples and for estimating with fair accuracy the absolute oxygen content of the individual samples.

The Beckman spectrophotometer equipped with standard 0.5 cm. cuvettes was used. Measurements were made at 660 m μ . At this wavelength the absorption coefficient of reduced hemoglobin is approximately five times that of oxyhemoglobin. The method operates on the principle that the difference in optical density between two samples of blood from the same subject having the same hemoglobin content is proportional to their difference in oxygen content. In practice the more highly oxygenated sample is used as the blank against which the other sample is read, thus eliminating the effect of "inactive" hemoglobin and other substances which do not alter their optical density with a change in oxygen tension. Samples are hemolyzed by a concentrated saponin solution before reading. Fifty-six gasometrically controlled determinations of A-V difference ranging from 0.5 to 15.0 volumes per cent have been made on

blood from nine different subjects. The standard deviation from regression is 0.23 volumes per cent. Estimate of the absolute oxygen content of a sample can be made by the additional colorimetric determination of the total hemoglobin. Satisfactory allowance can be made for a change in the hemoglobin concentration during the course of a study. In routine use the method is quite simple and has proved to be five to six times faster than the ordinary gasometric technic. The accuracy appears to be roughly equivalent to that of gasometric methods.

COMPARISON OF RESULTS OF MEASUREMENT OF RED BLOOD CELL VOLUME BY DIRECT AND INDIRECT TECHNIQUES. *William Parson, M.D., H. S. Mayerson, M.D., Champ Lyons, M.D., R. T. Nieset, M.D. (by invitation) and W. J. Trautman, Jr., M.D. (by invitation).* From The Departments of Medicine, Physiology and Surgery and the Laboratory of Biophysics, School of Medicine, Tulane University and the Alton Ochsner Medical Foundation, New Orleans, La.

Concomitant measurements of red blood cell volume and plasma volume were made with the radioactive phosphorus (P-32) technic and with the T-1824 method respectively in ten normal and thirty-five hospitalized individuals. A standard correction factor of 0.915 was used to correct the hematocrit values for trapped plasma. When this correction is used, the values calculated for red cell volume from the plasma volume and hematocrit data agree well with the values obtained by direct measurement of the red cell volume with the P-32 method. Total blood volumes calculated from the red cell and hematocrit and from the plasma volume and hematocrit show satisfactory agreement with the total blood volumes as calculated from the sum of the actually determined red cell and plasma volumes. Comparison of the (*in vitro*) peripheral and the body hematocrit also shows good agreement. The data suggest that the whole blood volume can be measured with an average discrepancy of less than 5 per cent by the plasma-dye-hematocrit method provided the corrected hematocrit value is used.

PLASMA VOLUME AND EXTRAVASCULAR THIOCYANATE SPACE IN EXPERIMENTAL SERUM

AUGUST, 1949

SICKNESS IN RABBITS. *George T. Harrell, M.D. and (by invitation) Ernest H. Yount, M.D.* From The Department of Internal Medicine, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.

Patients with Rocky Mountain spotted fever develop clinical edema during the acute phase of the disease. Frequently the plasma volume is reduced transiently and peripheral circulatory failure may ensue. The maximum changes usually occur just before the temperature begins to fall. The time relationships suggest the possibility that an antigen-antibody reaction may explain the pathogenesis of the alteration in capillary permeability. To test this thesis twelve rabbits were injected intravenously with 5 cc. Kg. of human plasma. The plasma volume was measured by the Evans blue technic and the thiocyanate space simultaneously determined by the loss of thiocyanate from the plasma. Three basic line determinations were made before injection; three additional determinations were made on successive days, beginning with the appearance of precipitins for human plasma in the rabbit's blood, usually on the seventh or eighth day after injection. A final determination was done one week later. A significant rise in the thiocyanate space was observed and was accompanied by clinical manifestations of serum sickness—edema, fever and listlessness. The drop in the plasma volume was small but was statistically significant for the group. The changes reverted to normal in convalescence. Similar results were obtained in a second group after the injection of purified human serum albumin.

STUDIES ON THE HEPATIC CIRCULATION IN HYPERTHYROIDISM. *J. D. Myers, M.D. (Introduced by Eugene A. Stead, Jr., M.D.)* From The Duke University School of Medicine, Durham, N. C.

A group of patients with clinically typical hyperthyroidism have been investigated in the fasting state in regard to total cardiac output, hepatic blood flow and splanchnic oxygen consumption. These measurements were made by the technic of venous catheterization. The data obtained were compared with a set of control data on subjects without significant disease.

The mean figures on eleven patients with

hyperthyroidism were as follows: metabolic rate, 54 per cent; cardiac index, 5.0; hepatic blood flow (BSP method), 920 ml. per minute per square meter of body surface; mixed arteriovenous oxygen difference, 4.4 volumes per cent; hepatic A-V oxygen difference, 6.8 volumes per cent and splanchnic oxygen consumption, 61 ml. per minute per square meter. Corresponding figures in twenty-seven control subjects were: cardiac index, 3.8; hepatic blood flow, 870; mixed A-V oxygen difference, 4.0; hepatic A-V oxygen difference, 4.3 and splanchnic oxygen consumption, 37. The splanchnic oxygen consumption in the controls comprised 23 per cent of the total oxygen consumption; in hyperthyroidism the corresponding figure was 30 per cent.

In summary, the patients with hyperthyroidism showed a moderate elevation in cardiac output without concomitant increase in hepatic blood flow. At the same time their splanchnic oxygen consumption was increased in proportion to the elevation in total metabolism. These circumstances require in hyperthyroidism an increase in oxygen extraction in the splanchnic area. This situation of an increased hepatic A-V oxygen difference in the fasting state is the same as that found in heart failure and may well play a significant role in the frequency of hepatic disease in thyrotoxicosis.

SOME FACTORS INFLUENCING SODIUM EXCRETION. *Jerry M. Lewis, M.D. and S. Maple Sevier, M.D. (Introduced by Tinsley R. Harrison, M.D.)* From The Department of Internal Medicine, Southwestern Medical College, Dallas, Tex.

The hourly urinary excretion of sodium has been studied in normal subjects under conditions of constant intake of water and sodium. Change from the recumbent to the sitting posture is accompanied by a sharp decline in sodium excretion. The usual duration of the lag period of this phenomenon suggests a chemical rather than a nervous mechanism. In the subjects thus far studied compression of the neck by a blood pressure cuff inflated to 25 mm. in a subject in the sitting position caused an increase in sodium excretion over that in a patient in the same position without the cuff.

The results taken together appear to indicate that: (1) some type of central mechanism may be a factor in regulation of sodium excretion and (2) the nature of this mechanism is still uncertain but it does not appear to be related to

alterations in cardiac output or in cerebral blood flow.

CHLORIDE BALANCE IN CONGESTIVE CIRCULATORY FAILURE. *Henry A. Schroeder, M.D.* From The Department of Internal Medicine, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo.

Forty patients suffering from congestive circulatory failure of cardiac origin were studied on a metabolic service for long periods of time. The intake of salt, calories and fluids was constant for varying intervals. The urinary output of chlorides was measured daily, over 2,200 determinations being made. Various procedures which alter the course of congestive failure were instituted after adequate control periods. (1) The amount of chlorides excreted in the urine was either depressed or was elevated very slightly when the intake of salt was increased, either by ingestion or by intravenous injection of a hypertonic solution. (2) Restriction of the fluid intake usually resulted in retention of chlorides and elevation of the intake sometimes initiated a chloride diuresis. (3) When the theoretical weight loss was calculated from the total urinary excretion of chlorides over several weeks and compared to the actual loss of weight, there was good agreement in about one-half the cases; in the other half there was an indication that the patients had been in a state of overhydration. Therefore, disturbances of both salt and water balance, separately and together, were present in cases of congestive failure. (4) Of the effects of diuretic agents, thcoalein was found to influence principally the excretion of water and the mercurial diuretics, the excretion of chlorides. Digitalis appeared to affect both but acted in only one-third of the patients. (5) Severe overhydration occurred in eighteen patients; this was accompanied by oliguria and dilution of plasma electrolytes. When electrolyte levels were elevated by intravenous injection of hypertonic saline, diuresis often became established. In these cases renal failure appeared to result from loss of extracellular sodium chloride. (6) When the urinary concentration of chlorides was considered in the light of other functions of the kidney, it appeared that the amount excreted was too low to be accounted for by diminution of renal blood flow and that extrarenal factors, presumably from the adrenal cortex and pituitary, were possibly operating.

MECHANISMS OF SALT AND WATER RETENTION IN HEART FAILURE. *D. J. Hughes, M.D. (by invitation), H. H. Turner, M.D. (by invitation), A. J. Moseley, M.D. (by invitation) and A. J. Merrill, M.D.* From The Emory University School of Medicine, Atlanta, Ga.

Much dissatisfaction has been expressed at the idea that retention of salt and water in heart failure is caused solely by the low renal filtration rate. The only explanation available for the fact that the tubules reabsorbed a larger proportion of the filtered sodium was their "fundamental sodium-conserving function." Many investigators have suspected an adrenal cortical effect as the reason. Conn's recent discovery of the inverse relationship between the sweat sodium concentration and activity of the sodium-retaining hormone of the adrenal cortex offered an excellent method of determining the activity of this hormone in heart failure. Four patients with cardiac failure were found to have low sweat sodium concentrations falling within the range of Cushing's disease. Three had a very low filtration rate and all had severe intractable failure. One had a normal filtration rate but he also had severe failure. Ten patients had a normal or high sweat sodium concentration. In two the renal plasma flow and filtration rate were not measured. In all but one of the remaining the filtration rate was either normal or only slightly reduced, the renal plasma flow was only moderately diminished and failure was much more easily controlled although twenty-four-hour sodium excretion was low on a 200 mg. sodium diet. The remaining patient had a very low filtration rate despite the fact that the renal plasma flow was well above the level at which the filtration rate was reduced. It was believed that he probably had had glomerulonephritis with perhaps a thickened Bowman's capsule. The fact that he retained sodium despite a normal sweat sodium suggests that reduced filtration played a part in the sodium retention. We have one other patient with a slight reduction in the renal plasma flow and filtration rate of 49 cc. per minute with intractable chronic heart failure. Her sodium retention was thought to be on a basis similar to that of the patient just mentioned. If patients with severe heart failure and edema are relieved of as much edema as possible with the

aid of mercurial diuretics, a fall in blood sodium concentration occurs sometimes to a level as low as 114 mEq. (normal 136 to 143). Despite this fall the patient does not lose his edema. While this could be due to an artificial imbalance between the proximal and distal convoluted tubules, it could mean that the posterior pituitary antidiuretic hormone is operating.

The exact time relationships between these phenomena in the course of heart failure is uncertain. Perhaps further work will clarify this.

INTRAVENOUS CATHETERIZATION OF THE HEART IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE. *Don W. Chapman, M.D. and Lloyd Gule, M.D. (Introduced by James A. Greene, M.D.)* From The Baylor University College of Medicine, Houston, Tex.

Recent advances in surgical alteration or correction of certain congenital defects of the heart and great vessels make it imperative that a more accurate diagnosis of such lesions be made. Intravenous catheterization of the heart has been a useful aid to ascertain the condition in patients suspected of having such congenital abnormalities.

A 6 French or 9 French special catheter is introduced into the median basilic vein and passed under fluoroscopic control via the subclavian vein and superior vena cava into the right side of the heart and into the pulmonary artery and its branches. The oxygen content of samples of blood are obtained at various sites and should not differ normally by more than 1.9 volumes per cent. Pressures in the various sites are recorded by means of a Hamilton manometer. This procedure has been used in fifty-eight patients with, or suspected of having, congenital defects of the heart or great vessels. The results illustrate its value to ascertain whether or not the patient has a defect, to indicate the operability when defects are discovered and to suggest the prognosis.

In cases of auricular septal defect the oxygen content of the blood from the right atrium is greater than that in the vena cava. In patients with ventricular septal defects a sufficient increase in oxygen content in the blood from the right ventricle is demonstrated when compared with that in the atrium. Septal defects may also be demonstrated by passing the catheter through the defect into the left side of the heart.

Patent ductus arteriosus is demonstrated by finding an increase in oxygen content of blood from the pulmonary artery as compared with the right ventricle and occasionally by an increased pulmonary arterial pressure. Cases of cyanotic congenital heart disease are presented showing the usual absence of the left to right shunt. Cyanotic patients with increased pressure in the right ventricle or pulmonary artery are discussed. Combined lesions such as cyanotic congenital heart disease with patent ductus arteriosus may be found and patients with such abnormalities are described. Several patients who were suspected of congenital defects but in whom the catheterization studies were normal are described. A case in which a pulmonary vein was found to empty into the right (?) or common (?) atrium is reported. Complications of the procedure, including premature ventricular contractions, phlebitis and venospasm, are described.

DIRECT ARTERIAL PUNCTURE AND PHOTO-ELECTRIC PLETHYSMOGRAPHY IN THE DIAGNOSIS OF COARCTATION OF THE AORTA.
Melvin L. Goldman, M.D. (by invitation) and Henry A. Schroeder, M.D. From The Department of Internal Medicine, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo.

In thirteen patients with coarctation of the aorta photoelectric plethysmograms were made of the pulses in the ears, toes, fingers and scrota, and the blood pressure in the brachial and femoral arteries was measured with a Hamilton manometer. By these means it was possible to determine roughly the degree of constriction of the aorta. In eleven of the patients femoral diastolic pressures were the same or slightly less than that in the brachial. In the others it was considerably lower. Both groups showed severe constriction of the aorta at operation. Diastolic pressure was elevated in only two; one showed a minimal constriction of the aorta by retrograde aortic arteriography which was reflected by a slightly lower systolic pressure in the femoral artery than in the brachial. The pulse wave velocity was found in all patients but one to be considerably less than normal. Two subjects were studied after surgical correction of the defect; the changes observed were in the direction of normal, the pulse wave velocity returning to normal values.

The mechanism of hypertension in coarctation was investigated by partial constriction of the brachial artery to a point above diastolic pressure by means of a cuff and the blood pressure measured below the constriction. When this was done in normal subjects and in those with coarctation or hypertension, both systolic and diastolic pressures rose significantly above control values, the rise occurring on the next systole. This unusual finding may be the result of the "breaker phenomenon" or may account, in part, for the hypertension observed in these patients.

In the course of these studies four female patients were found to exhibit coarctation, hypogonadism, short stature and shortening of one or more phalangeal, metatarsal or metacarpal bones. The frequency of this combination of findings apparently has not been noted previously.

REVERSAL OF THE LEFT VENTRICULAR STRAIN PATTERN OF THE ELECTROCARDIOGRAM BY ETAMON AND SPINAL ANESTHESIA
Arthur Ruskin, M.D. and Alfred Lane, M.D. (Introduced by Raymond Gregory, M.D.)
 From The University of Texas Medical Branch, Galveston, Tex.

Hypertensive patients with the left ventricular strain pattern in the electrocardiogram show variability in the latter at different times. This variability has not correlated well with the level of the blood pressure. On the other hand, sympathectomized hypertensive patients have presented, parallel to their relative hypotensive states, favorable changes (toward normal) in the electrocardiogram in about 50 per cent of the cases.

Tetraethyl ammonium, 0.5 Gm. intravenously, usually causes a marked temporary drop in the systolic and diastolic blood pressures of hypertensive patients. Electrocardiograms obtained in the horizontal position at the minimum levels of blood pressure in such cases showed marked elevations of the T waves and frequently of the depressed S-T segments. In other cases showing lesser drops of blood pressure electrocardiograms taken in the sitting posture, with concomitant greater drops in blood pressure, sometimes caused partial reversal of the left ventricular strain pattern.

Spinal anesthesia likewise caused normalization of the electrocardiogram if the blood

pressure fell markedly. No correlation could be established between degrees of drop in blood pressure and the degrees of reversal of the strain pattern. Such electrocardiographic changes could not be obtained following sodium amytal although the high blood pressure fell, albeit slowly. Etamon lower pressures in non-hypertensive individuals elevated the T waves only in exceptional cases. The possible mechanisms will be discussed at a future date.

ROLE OF THE KIDNEY IN THE PATHOGENESIS OF EXPERIMENTAL HYPERTENSION. *Arthur Grollman, M.D., John Vanatta, M.D. (by invitation) and E. E. Muirhead, M.D.* From The Department of Physiology and Pharmacology, Pathology and Experimental Medicine, Southwestern Medical College, Dallas, Tex.

By application of the artificial kidney to nephrectomized dogs or those in which one ureter was implanted into the small intestine and the contralateral kidney removed it has been possible to determine the role played by the kidney in the pathogenesis of hypertension. In the absence of both kidneys the blood pressure rises gradually, reaching hypertensive levels within the course of a week. If kidney tissue deprived of its excretory function by implantation of the ureter into the gut remains in the body, the animal remains normotensive. These experiments demonstrate the erroneous-ness of the view that hypertension is the result of the elaboration of a pressor agent (renin, angiotonin, hypertension) by the kidney and prove that the kidney normally performs some incretory function which, when in abeyance, results in the development of hypertension.

EFFECTIVENESS OF SEVERAL ADRENOLYTIC, SYMPATHOLYTIC OR GANGLIONIC BLOCKING DRUGS AGAINST ACUTE AND CHRONIC NEUROGENIC HYPERTENSION. *K. S. Grimson, M.D. and (by invitation) J. R. Chittum, M.D.* From The Department of Surgery, Duke University School of Medicine, Durham, N. C.

Prisol, dibenamine and two newer sympatholytic drugs, to be presented as C 7337 and C 5968, and also two ganglionic blocking drugs, etamon and a new product SC 1950, have been tested against increased intracranial pressure

acutely produced in anesthetized dogs and against chronic neurogenic hypertension in dogs.

In increased intracranial pressure experiments dogs under chloralose anesthesia were given progressively larger doses of one test drug intravenously until bilateral occlusion of the carotid arteries no longer significantly increased the blood pressure. Intracranial pressure was then increased by forcing saline through a trochar into the skull. Increase of intracranial pressure in untreated animals stimulated increases of blood pressure to values exceeding 200 mm. Hg. In treated animals the blood pressure gradually decreased during drug administration, occasionally reaching levels below 70 mm. Hg. Increase of intracranial pressure then usually effected only moderate increase of the blood pressure. Two of the six drugs, priscol and C 7337, in occasional experiments completely blocked the pressor response.

Each of the six drugs was also tested in dogs with chronic neurogenic hypertension persisting one to twelve months after excision of the carotid sinuses and division of the depressor nerves. The blood pressure was obtained before and several times during a three to eight-hour period after administration of the test drug. Priscol was given orally, intramuscularly and also intravenously. Etamon, SC 1950, C 7337 or C 5968 were given intravenously and also intramuscularly. Dibenamine was given intravenously only. Three or more tests were performed for each route of administration. The effect of priscol was variable, pressor responses occurring occasionally, and a significant to normal reduction of blood pressure in one-half of the experiments also occurring. Dibenamine caused reduction of the pressure to normal and this lasted fifty hours in one dog. C 7337 and C 5968 reduced the blood pressure to normal. Etamon reduced the pressure to normal in one-half of the trials while GD 1950 had the same effect in all animals but one. In unanesthetized normal animals the aforementioned drugs caused changes in blood pressure varying from an increase to moderate decrease.

EFFECT OF HIGH SPINAL ANESTHESIA ON THE CARDIAC OUTPUT OF NORMAL AND HYPERTENSIVE PATIENTS. *Lawrence G. May, M.D., Alene Bennett, M.D., A. L. Lane, M.D., E. D. Futch, M.D., Mary Lynn-Schoomer, M.D. (by invitation) and Raymond Gregory,*

M.D. From The University of Texas Medical Branch, Galveston, Tex.

In attempting to arrive at some understanding of the pathogenesis of essential hypertension, high spinal anesthesia has been used as a method of producing a decrease in blood pressure in patients with essential hypertension. The degree to which elevated blood pressure may be lowered uniformly with high spinal anesthesia has suggested the importance of an increased vasomotor tone in maintenance of the arteriolar constriction. Opponents to this idea have argued that the drop in blood pressure is due to diminished venous return to the heart which produces a decrease in the cardiac output sufficient to explain the fall in blood pressure.

Other studies of the relationship between venous and arterial pressure under high spinal anesthesia have shown no correlation in the time relationships between the falls of venous and arterial pressures. In most instances the arterial pressure falls before the venous pressure. From this somewhat indirect evidence it has been believed that the fall in arterial pressure cannot be explained on the basis of diminished cardiac output. It was decided, however, that cardiac output studies must be done in order to make final conclusions and such studies were made employing the direct Fick method.

One hundred seventeen cardiac output determinations have been done on fifteen normotensive and seven hypertensive individuals: (1) Unsedated normotensives with spinal anesthesia, (2) sedated normotensives with spinal, (3) unsedated normotensives without spinal, (4) sedated normotensives without spinal, (5) sedated hypertensives with spinal, (6) unsedated hypertensives with spinal, (7) sedated hypertensives without spinal, (8) unsedated hypertensives without spinal.

In the normotensive patients the control cardiac indices before spinal anesthesia are so high and so variable that it is impossible in most instances to get a base line within the normal range. In this group spinal anesthesia causes a fall in the cardiac index but the fall is always within the normal range. In the sedated normotensives the control cardiac indices are essentially within the normal range; spinal anesthesia causes some slight fall but the fall is essentially within the normal range. We were somewhat surprised to find the cardiac indices

of unsedated hypertensives to be uniformly within the normal range and often to be below the commonly accepted normal range, and to find that the sedated hypertensive individual often has a slightly higher cardiac index than the unsedated.

In the sedated hypertensives with high spinal anesthesia there was little if any fall in the cardiac index in spite of a uniformly obtained fall in both systolic and diastolic blood pressure. The falls in cardiac index that did occur in the hypertensive group were usually still within normal range and were no greater than the falls which occurred in the control groups of hypertensives which were sedated; a spinal tap was done but no spinal anesthesia was induced. Hypertensive patients under spinal anesthesia uniformly had higher cardiac indices than a group without spinal anesthesia.

In normotensives high spinal anesthesia associated with the fall in blood pressure may not be associated with a significant fall in cardiac index if the control values are within normal limits before the spinal anesthesia is induced unless the blood pressure falls below critical levels of 80 to 90 mm. Hg systolic. In the hypertensive group, use of a high spinal anesthesia which is associated with a great fall in the blood pressure, we usually did not find a significant fall in the cardiac index. The variations which occurred were usually within the normal range.

In both normotensive and hypertensive individuals significant falls in blood pressure may occur without any significant fall in cardiac index.

Read by Title

OBSERVATIONS ON REGULATION OF THE CEREBRAL CIRCULATION. *Peritz Scheinberg, M.D. (by invitation) and Eugene A. Stead, Jr., M.D.* From Duke University School of Medicine, Durham, N. C.

The purpose of this study was to determine the ability of the cerebral blood vessels to dilate and constrict in response to various physiologic and pathologic situations. The cerebral blood flow was measured by the nitrous oxide method of Kety and Schmidt. The cerebral O_2 and glucose consumptions were calculated by multiplying the respective arterio-internal jugular differences by the cerebral blood flow. The peripheral resistance was calculated in absolute

units by dividing the mean pressure by the blood flow.

Observations have been made in normal subjects in the recumbent position and after motionless standing. Patients with hypertension who have recovered from removal of the sympathetic chain from I₁ through the stellate ganglia were studied in the recumbent and standing positions. The effects of stellate block in patients with cerebral vascular disease have been observed.

IMPROVEMENT OF THE ARTIFICIAL KIDNEY:

AN EXPERIMENTAL STUDY OF ITS APPLICATION TO DOGS DEPRIVED OF RENAL EXCRETORY FUNCTION. *John Vanatta, M.D. (by invitation), E. E. Muirhead, M.D. and Arthur Grollman, M.D.* From The Departments of Physiology and Pharmacology, Pathology and Experimental Medicine, Southwestern Medical College, Dallas, Tex.

The artificial kidney has been applied 120 times to eighty-five dogs, seventy-five of which were deprived of renal excretory function by bilateral nephrectomy or other procedures. Study of the technic as described by Kolff and other workers revealed the following fundamental defects: (1) the composition of the bath not only failed adequately to maintain the normalcy of the chemical composition of the blood but in addition produced hemolysis; (2) the membrane reacted with blood to cause hemolysis; (3) the pump on the original apparatus of Kolff caused hemolysis; (4) the dosage of heparin had to be adjusted, and antiheparin substances were needed to prevent hemorrhage from the wound and (5) variations in the blood content of the apparatus resulted in depletion or overload of the vascular system.

Following alteration of the bath and chemical treatment of the membrane as well as attention to other details, nephrectomized dogs were maintained to the twentieth day and dogs otherwise deprived of renal excretory function for a period of a month, at which time they were sacrificed for pathologic study.

PATHOLOGIC CHANGES IN BILATERALLY NEPHRECTOMIZED DOGS WITH HYPERTENSION. *E. E. Muirhead, M.D., John Vanatta, M.D. (by invitation) and Arthur Grollman,*

M.D. From The Departments of Physiology and Pharmacology, Pathology and Experimental Medicine, Southwestern Medical College, Dallas, Tex.

Bilaterally nephrectomized dogs sustained with the artificial kidney develop a characteristic pattern of lesions. Early changes occur by the fifth day, definite lesions by the eighth day and advanced lesions thereafter. The main changes are found in smooth muscle tissue throughout the body. Arteries, veins and arterioles display the following: loss of longitudinal striations, hyaline swelling, pyknosis, disappearance of nuclei and confluence of hyalinized fibers with a smudgy appearance. Infarcts are noted in the myocardium, gastrointestinal mucosa and intestinal muscularis. Smooth muscle changes are also noted in the muscular coats of the esophagus, stomach, small and large intestine, splenic trabeculae and urinary bladder. The bronchial tree and pulmonary vessels do not reveal these changes. Hyaline emboli are encountered in the heart, gastrointestinal mucosa and lungs. Bilateral ligation of the ureters culminate in similar findings. Implantation of the ureter into the small bowel with contralateral nephrectomy and sustenance up to thirty days has not caused these changes.

The vascular changes are those of malignant hypertension. Widespread smooth muscle tissue changes seem evident in this condition.

HEMATOLOGIC ABNORMALITIES RESULTING FROM METASTASES OF PROSTATIC CARCINOMA TO BONE MARROW. *U. Jonsson, M.D. (by invitation) and R. W. Rundles, M.D.* From The Duke University School of Medicine, Durham, N. C.

The growth of tumor metastases within the bone marrow may produce fever, skeletal pain. roentgenologically demonstrable bone lesions and/or anemia before there is local evidence of neoplastic growth. Hematologic studies may establish the diagnosis and aid in evaluating the response to therapy.

Bone marrow aspirations in twenty-eight patients with prostatic cancer, nineteen of whom had x-ray or other evidence of tumor metastases, revealed tumor implants in sixteen subjects. Among those with metastases the prostate gland was considered by palpation to be benign in four cases. Five had questionable neoplastic

nodules. Osteoblastic skeletal lesions were present in fourteen patients. The acid phosphatase was above 3 King-Armstrong units in sixteen and the alkaline phosphatase above 10 King-Armstrong units in seventeen patients. A useful physical sign—pronounced tenderness over the sternum—was present in thirteen of those with marrow metastases.

The hemoglobin was less than 12 Gm./100 cc. in sixteen patients. Severe anemia of the leuko-erythroblastic type, with immature granulocytes and nucleated red blood cells in the circulating blood, was present in eight patients with gross infiltration of the bone marrow with tumor tissue. Tumor cells were found in the bone marrow of two patients who had no x-ray abnormalities and normal phosphatase and peripheral blood values.

Six of the patients with leuko-erythroblastic anemia associated with tumor metastases in the bone marrow were followed for four to eleven months after orchidectomy and estrogen therapy. The peripheral blood values improved or became normal in five months. Tumor cells in the bone marrow decreased in number, their cytoplasm became denser and the nuclei pyknotic. Progressive bony sclerosis of a degree making needle biopsy impossible was observed without development of anemia. The degree of tumor infiltration increased in one patient and the blood values continued to fall.

EFFECT OF ADRENOKYL ON BLOOD LOSS FROM SURGICAL WOUNDS. *J. J. Zaverbnik, M.D., R. F. Hagerty, M.D. (by invitation) and K. S. Grimson, M.D.* From The Department of Surgery, Duke University School of Medicine, Durham, N. C.

Adrenoxyl, a mono-semicarbazone of adrenochrome, reportedly decreases bleeding time of rabbits and man. Our studies confirm the effect on bleeding time. In dogs an intramuscular injection of 10 gamma of adrenoxyl produced a marked decrease, the effect becoming maximal at thirty to sixty minutes. A study of the ability of the drug to decrease blood loss from surgical wounds also has been made.

Consecutive parallel and apparently similar incisions were made in the liver of anesthetized dogs estimating bleeding by weight of the blood collected. One hour after administration of 10 gamma of adrenoxyl bleeding decreased markedly with one exception in which it was

apparent that severance of a large vessel increased bleeding and masked the effect of adrenoxyl.

The amount of blood loss from wounds produced by the resection of similar portions of a rabbit's ear was also estimated and was found to be decreased moderately one hour after administration of 10 gamma of adrenoxyl. This effect was measured by producing the same type of wounds on opposite ears of the same rabbit five days apart. Three different wounds produced on one ear before administration of the drug bled an average of .31 Gm., .72 Gm., .80 Gm. of hemoglobin, respectively, increasing amounts representing the larger or more proximal incisions. Five days later three similar wounds were made using the opposite ear and administering adrenoxyl. Decrease in bleeding after administration of adrenoxyl was 44.7 per cent, 3.7 per cent and 13.3 per cent, respectively. The effect of adrenoxyl appeared more marked in wounds in which bleeding was predominantly from small vessels. An attempt was also made to study the amount of bleeding from donor sites of skin grafts and from multiple skin incisions, but wide variations of bleeding occurring in control studies prevented studying the effects of adrenoxyl on blood loss from these wounds.

Adrenoxyl appears to decrease the bleeding time and amount of blood loss from wounds in which the bleeding is a slow, steady ooze. Because of encouraging results obtained so far, clinical trials have been started and will be discussed at a future date.

CIRCULATING RED CELL MASS IN POLYCYTHEMIA VERA AS DETERMINED BY RED BLOOD CELLS TAGGED WITH THE RADIOACTIVE ISOTOPE OF IRON. *George R. Meneely, M.D., E. B. Wells, M.D. (by invitation) and Paul F. Hahn, M.D.* From The Department of Medicine, Vanderbilt University School of Medicine and the Cancer Research Laboratories, McHarry Medical College, Nashville, Tenn.

Previous reports by ourselves and others have shown a pronounced difference between antecubital venous hematocrit and the average body hematocrit when the plasma volume is measured by the method of Gibson and Evans and the red cell mass by the method of Hahn, Ross, Balfour, Bale and Whipple as modified by Meneely, Wells and Hahn. Although under

normal conditions it is true that the venous hematocrit reflects proportionately the circulating red cell mass, in conditions such as inanition, shock, cardiac failure, polycythemia vera, etc., such a relationship probably does not occur and the venous hematocrit does not afford a

TABLE I

Patient	Weight	Red Blood Cells	Hematocrit (vol. %)	Red Cell Mass (ml.)			
				Normal	Estimated	Determined	Excess
J. W..	85	10.8	67	2300	3400	6200	2800
C. Y..	70	8.0	61	1890	2560	3960	1400

true picture of the existing state of affairs in the circulation. We present data in two patients to show that by direct determination the total circulating red cell mass is considerably greater than that which would be estimated on the basis of body weight and venous hematocrit.

From this data it is seen that the observed red cell mass is much greater than would be expected on the basis of antecubital venous hematocrit and body weight. We believe that many failures in therapy of polycythemia by phlebotomy are ascribable to a lack of comprehension of the extent of the plethora and polycythemia actually present which leads to gross undertreatment. Properly employed, phlebotomy is a physiologic and adequate therapy. Such is not the case with phenylhydrazine which incites reticulocytosis, is toxic and releases detritus in the vascular bed of patients already threatened with thrombotic accidents. We have stated before and reiterate our opposition to radioactive phosphorus in this condition, which is almost invariably benign, because we believe phosphorus as a relatively long-lived isotope is not suitable for therapy and because of the danger of precipitating a fulminating leukemia.

DEMONSTRATION OF ADRENOCORTICOTROPIC HORMONE IN THE URINE OF TWO FEMALE PATIENTS WITH CUSHING'S SYNDROME. *Albert Segaloff, M.D. and William Parson, M.D.* From The Department of Medicine, Tulane University School of Medicine, and the Alton Ochsner Medical Foundation, New Orleans, La.

Two female patients with classical Cushing's syndrome have been studied. They both fitted

the usual criteria with thin skin, striae, atrophic muscles, plethoric facies, "buffalo obesity," hypertension, etc. In addition they had markedly elevated urinary excretions of cortin (biological assay) and one of them had an (intermittently) elevated urinary excretion of 17-ketosteroids. This latter patient died from an overwhelming infection of *Cryptococcus hominis*. The post-mortem examination revealed bilateral adrenal cortical hyperplasia and Croke cell changes in the pituitary. The other patient is still under observation and it is believed that she, too, has bilateral adrenal cortical hyperplasia.

The assays for adrenotrophic hormone in the urine were done by the Sayers and Sayers technic based on depletion of adrenal ascorbic acid in hypophysectomized rats. The most satisfactory urinary concentrates were achieved by a modified alcohol precipitation dialysis method. In the best studies the animals each received intravenously the concentrate from twelve hours of urine.

Urinary concentrates from normals and from patients with various diseases were assayed in parallel with the concentrates from patients with Cushing's syndrome. The controls were consistently negative. (The controls included patients with proven adrenal cortical hyperplasia with virilism, "the adrenogenital syndrome.")

The two patients reported here represent the only instances we have found of unequivocal evidence of urinary excretion of adrenocorticotrophic hormone.

SERUM CHOLESTEROL ESTERASE IN NORMAL DIABETIC AND ARTERIOSCLEROTIC PATIENTS. *E. D. Futch, M.D. (by invitation) and Raymond Gregory, M.D.* From The University of Texas Medical Branch, Galveston, Tex.

In early atherosclerotic changes cholesterol esters exceed free cholesterol. In old atherosclerotic deposits the percentage of free cholesterol increases. The degree to which cholesterol esterase activity might be a factor in the intimal deposition of cholesterol or its esters is the basis for the studies that are being reported here.

In vitro studies of the extent and rapidity of the conversion of free cholesterol to cholesterol esters resulting from the incubation of serum in ten normal, ten diabetic and ten patients with severe arteriosclerotic disease have been made according to the method of Sperry. Serum from

the aforementioned types of patients was analyzed for cholesterol fractions at zero hours and after twenty-four, forty-eight and seventy-two hours incubation at 37°C. under sterile conditions. The rate and degree to which free cholesterol was converted to cholesterol esters varied within wide limits. We were, however, unable to detect any significant change in these values in the normal diabetic and arteriosclerotic groups. From these data it is concluded that abnormalities of serum cholesterol esterase do not play a significant role in the pathogenesis of atherosclerosis.

EFFECTS OF A QUATERNARY AMINE ON FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM. *F. H. Longino, M.D. (by invitation), J. R. Chittum, M.D. (by invitation) and K. S. Grimson, M.D.* From The Department of Surgery, Duke University School of Medicine, Durham, N. C.

Effects of 2,6 dimethyl diethyl piperidinium bromide on functions of the autonomic nervous system have been determined. In anesthetized dogs the drug lowered arterial blood pressure and blocked changes of pressure normally occurring with the carotid sinus reflex, stimulation of central and peripheral ends of divided vagi and anoxia. It also equalized changes of peripheral resistance of normal and sympathetomized extremities during these stimuli. Pressor responses to intravenous epinephrine were apparently increased. Terminal increase of blood pressure normally associated with acute rise of intracranial pressure was not prevented. Effects of the drug were counteracted by prostigmine.

In normal unanesthetized dogs moderate increases of blood pressure and tachycardia occurred after administration of the drug. In dogs with chronic neurogenic hypertension the drug caused a reduction of blood pressure and a slowing of the pulse. Barium studies of the gastrointestinal tracts of normal dogs showed that small doses stimulated gastric and intestinal activity but that larger doses effected cessation of peristalsis of the stomach and delayed transit through the small intestine.

In patients the drug abolished activity of the stomach and small intestine as shown by balloon intubation studies. Barium studies demonstrated delay of gastric emptying and of transit through the small intestine. Effects on the gastrointestinal tract were partially counter-

acted by urecholine. In normotensive patients a transient fall of blood pressure occurred. This was more marked and prolonged in hypertensive patients. Reduction or reversal of normal pressor responses to breath holding or application of cold was effected as was loss of the temperature gradient of each extremity, paralysis of accommodation, dilatation of the pupils and ptosis of the upper eyelids.

Actions of this new drug were apparently much like those of the tetraethylammonium ion, and since these actions were reversed by prostigmine it seems likely that cholinergic synaptic transmission through autonomic ganglia is blocked.

RESPONSE OF LINGUAL MANIFESTATION OF PERNICIOUS ANEMIA TO PTEROYLGLUTAMIC ACID AND VITAMIN B₁₂. *James F. Schieve, M.D. (by invitation) and R. W. Rundles, M.D.* From The Duke University School of Medicine, Durham, N. C.

While the therapeutic effectiveness of synthetic pteroylglutamic acid is satisfactory in the majority of patients with pernicious anemia, macrocytic anemia often is not completely corrected and neurologic relapses may occur on maintenance doses. Little attention has been paid to the third major clinical manifestation of the disease, that of atrophy and inflammation of the lingual mucosa.

Seven patients with pernicious anemia in relapse having lingual mucosal atrophy were given 30 to 100 mg. of pteroylglutamic acid daily by mouth. In two the filiform papillae regenerated to normal height in seven to ten days, a response equal to that regularly obtained by fully potent liver therapy. In five patients the lingual response from the beginning of therapy was poor. Their tongues tended to remain red and the papillae stubby. During the third month of pteroylglutamic acid therapy two of these patients had definite lingual relapses, developing sore, red and completely smooth tongues. They were given intramuscular injections of 0.010 and 0.025 mg. of vitamin B₁₂. Regeneration of filiform papillae and restoration of the normal lingual color followed in six to seven days.

Five patients with untreated pernicious anemia in relapse who also had lingual manifestations of the disease were given 0.001 mg. daily or a single dose of 0.010 mg. of vitamin

B₁₂. Regeneration of the papillae and restoration of a normal lingual color followed in six to ten days.

Pteroylglutamic acid may fail to induce and maintain remissions of lingual manifestations of pernicious anemia as well as the anemic and neurologic manifestations. Vitamin B₁₂ produced rapid regeneration of the lingual mucosa in patients with pernicious anemia who relapsed under pteroylglutamic therapy and in those who had no previous treatment.

VIRUS ISOLATION AND SEROLOGIC STUDIES IN PATIENTS WITH CLINICAL MUMPS. *William F. Friedewald, M.D. (introduced by Paul B. Beeson, M.D.)* From The Department of Bacteriology and Immunology, Emory University School of Medicine, Atlanta, Ga.

Materials from patients with various manifestations of mumps were tested for virus by the amniotic method of inoculation into embryonated eggs. Mouth washings from seventeen patients obtained within three days after the onset of parotitis yielded virus in ten of the specimens (59 per cent). Virus was also recovered from the testicular tissue of one patient with orchitis. Virus was not detected in (1) the saliva from three patients which was taken seven days after the onset of parotitis, (2) the spinal fluid of seven patients with meningoencephalitis, (3) hydrocele fluid of two patients with orchitis, (4) the blood of three patients taken during the first or second day of illness and (5) a placental extract from a patient with parotitis.

Agglutination inhibition and complement fixation tests on sera from fifteen patients with parotitis showed comparable rises in the titer of the antibodies. The complement fixation test, however, appeared to be more reliable and gave more reproducible results. No major differences in the antigenic structure of a stock strain of mumps virus and two viruses isolated in the present work were apparent in the tests with human sera or with antisera prepared in chickens against these viruses.

STUDIES IN THE FRACTIONATION OF LIVER.

COMPOSITION OF REGENERATING LIVER AFTER PARTIAL HEPATECTOMY IN RATS.

Alfred Chanutin, M.D. and (by invitation) Erland C. Gjessing, M.D. From The De-

partment of Biochemistry, University of Virginia School of Medicine, Charlottesville, Va.

The rate of regeneration of the liver following partial hepatectomy is greatest during the second, third and fourth days as judged by the wet and dry weights and nitrogen contents. The percentage concentration of the total solids decreases during the first three postoperative days. The respective control values are not reached by the fourteenth day.

A procedure is described for fractionating liver into three fractions: (A) a saline insoluble residue; (B) a precipitate obtained from the dialyzed saline extract at pH 5.8 and (C) ethanol-precipitated proteins.

The total solid and nitrogen contents of each of the three fractions are decreased to the same extent on the first postoperative day and increase at approximately the same rate on subsequent days. During the first and second postoperative days excessive amounts of lipid are present in Fractions A and B. Subsequently the lipides are incorporated in these two fractions in about the same proportions noted for nitrogen. Fraction C contains traces of lipid carbon and is devoid of cholesterol. The total lipid carbon and cholesterol concentrations of the liver mitochondria are not affected by partial hepatectomy. The respective relative proportions of the total solids, nitrogen and total lipid in the three liver fractions are relatively constant during liver regeneration.

The conclusion to be drawn from this investigation is that the major components of three distinctly different liver fractions are regenerated at approximately the same rate following partial hepatectomy.

LACK OF PITUITARY GONADOTROPHINS ASSOCIATED WITH ADRENAL ANDROGEN DEFICIENCY. *Laurence H. Kyle, M.D. (Introduced by Harold Jeghers, M.D.)* From The Department of Medicine, Georgetown University School of Medicine, Washington, D. C.

A negro female, nineteen years of age, showed primary amenorrhea, hypogenitalism, lack of mammary development, absence of axillary and pubic hair and eunuchoid skeletal proportions, the ratio of trunk to lower extremities being .92. Additional findings were a number of

congenital defects including an arteriovenous fistula of the left forearm, nystagmus, partial optic atrophy and moderate cardiac enlargement. There was no family history of any similar disorder. Laboratory examination revealed pituitary gonadotrophins negative for 6 mouse units and urinary 17-ketosteroids averaging 1.5 mg. per twenty-four hours. Glucose tolerance test and insulin tolerance tests were normal. The basal metabolic rate was within normal limits. On the basis of these findings it was decided that the patient fitted none of the usual groups associated with hypogonadism. Considered probable was a diagnosis of primary gonadotrophin deficiency together with deficiency of whatever trophic hormone stimulates adrenal androgen production. Search of the literature revealed a report of one similar case.

The pattern of the disease appeared suitable for testing the postulation of Albright and Reifstein in regard to stimulation of adrenal androgen production by the luteinizing hormone. Consequently the patient was studied from several viewpoints during administration of large amounts of luteinizing hormone in the form of chorionic gonadotrophin (A.P.L.).

During her course of therapy the patient showed quite marked breast development together with cornification of previously atrophic vaginal epithelium. Such evidence of estrin production is not in accordance with our present concepts of action of chorionic gonadotrophin. Possible explanations of these changes will be discussed at a later date.

VITAMIN B₁₂, PTEROYLGLUTAMIC ACID AND LIVER EXTRACT IN THE TREATMENT OF MACROCYTIC ANEMIA. *Grace A. Goldsmith, M.D.* From The Department of Medicine, Tulane University School of Medicine, New Orleans, La.

An increase in reticulocytes, erythrocytes and hemoglobin followed administration of vitamin B₁₂ to six patients and pteroylglutamic acid to twenty-four patients with macrocytic anemia in relapse. Findings will be compared with the response to liver extract. A normal or slightly subnormal blood picture was maintained in twelve patients for more than six months with 5 mg. of pteroylglutamic acid daily. Doses of 2.5 mg. per day were equally effective in two patients with sprue and two with nutritional macrocytic anemia, but the blood count fell

in two patients with pernicious anemia. Liver extract, 15 to 30 units weekly, maintained the erythrocyte count and hemoglobin at higher levels than did 5 to 30 mg. of pteroylglutamic acid daily in four or five patients. Substitution of vitamin B₁₂ for pteroylglutamic acid in one patient was followed by improvement in the blood picture.

Of nine patients with pernicious anemia treated with pteroylglutamic acid two developed a neurologic relapse during therapy while existing neurologic changes in two others were unaffected. Neurologic abnormalities were reversed by vitamin B₁₂ in one patient who received this therapy.

ROLE OF THE KIDNEY IN THE STORAGE OF IRON. *John K. Hampton, Jr., M.D. (Introduced by H. S. Mayerson, M.D.)* From The Department of Physiology, Tulane University School of Medicine, New Orleans, La.

Studies by Granick and others have shown that iron is stored chiefly in the liver, spleen and bone marrow as the protein-iron compound, ferritin. Evidence is also available to indicate the presence of ferritin in crystallizable amounts in the kidneys of the cat and the dog. Its presence in the horse kidney has been demonstrated in minute amounts.

The present experiments extend these findings to the mouse and rabbit kidney. Attempts to crystallize ferritin by the CdSO₄ method from animals using the usual laboratory regimen were unsuccessful. However, when hemoglobin or iron compounds were injected intraperitoneally, large amounts of ferritin appeared in the mouse kidneys and in some of the rabbit kidneys. The amount of ferritin present appeared to be correlated with the dose of iron administered. The significance of these findings is being investigated.

EFFECT OF METHADON ON ERYTHROCYTE PERMEABILITY IN VITRO AND ITS POSSIBLE CONNECTION WITH CHOLINESTERASE ACTIVITY. *Margaret E. Greig, M.D. and (by invitation) William C. Holland, M.D.* From The Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tenn.

In some metabolic studies *in vitro* in this laboratory it was found that methadon (amidone) inhibited glycolysis of glucose by the rat brain. It was also found to inhibit cholinesterase activity.

In some experiments *in vivo* on dogs it was found that intravenous administration of methadon was frequently but not always followed by a hemoglobinuria. This was accompanied by an increase in erythrocyte fragility. In some experiments *in vitro* methadon also produced an increase in fragility of erythrocytes. This increase in fragility of erythrocytes might be due to the inhibition of glycolysis by methadon, as Wilbrandt reported changes in permeability of erythrocytes exposed to sodium fluoride or to sodium iodacetate which are known to be glycolytic inhibitors. However, sodium fluoride and sodium iodoacetate also inhibit cholinesterase activity in the concentrations used by this author and it would seem possible that inhibition of this enzyme might be involved in the changes observed. To test this possibility the effects of prostigmine and physostigmine, which are specific inhibitors of cholinesterase, were investigated and it was found that these drugs also produced changes in permeability of erythrocytes. The results of these experiments with physostigmine and prostigmine as well as those with methadon seem to indicate that inhibition of cholinesterase activity, rather than or in addition to inhibition of glycolytic enzymes, may be involved in changes in permeability of the erythrocyte membrane. Experiments on the changes in cation concentration of erythrocytes exposed to methadon and other inhibitors of cholinesterase are in progress.

DETERMINATION OF CIRCULATING RED BLOOD CELL VOLUME WITH RADIOACTIVE PHOSPHORUS. R. T. Nieset, M.D., Blanche Porter, M.D., W. S. Trautman, Jr., M.D., Ralph M. Bell, M.D. (by invitation) and William Parson, M.D., Champ Lyons, M.D. and H. S. Mayerson, M.D. From The Laboratory of Biophysics, Departments of Medicine, Surgery and Physiology, School of Medicine, Tulane University and the Alton Ochsner Medical Foundation, New Orleans, La.

A simple dilution method for direct measurement of total circulating red blood cell volume using radioactive phosphorus (P-32) has been

developed. The red cells from the subject of study are utilized for labelling. Whole blood samples are used for counting so that no chemical or physical separation of the trace element is required. The validity of the method has been proved by independent studies in patients of the rate of absorption and of loss of radioactive phosphorus by red cells *in vivo* and *in vitro* and of the loss of phosphorus from the plasma *in vivo*. These experiments show that the P-32 is taken up rapidly by red cells and released slowly. The ease of counting and opportunity for repetitive measurement have proved to be advantageous in the clinical exploitation of the method.

IN VITRO PROPERTIES OF CORYNEBACTERIUM DIPHTHERIAE STRAINS ISOLATED FROM DIPHTHERIA PATIENTS IN LOUISIANA. M. F. Shaffer, M.D. From The Department of Bacteriology, Tulane University School of Medicine, New Orleans, La.

Several European workers have observed a fair degree of correlation between the clinical severity of diphtheria cases in local outbreaks and the varieties of *C. diphtheriae* (gravis, intermedius and mitis) responsible. American investigators have hitherto been unable to demonstrate a similar relationship for the organisms isolated from diphtheria patients in this country. Gravis strains have been obtained from healthy carriers in certain of the Southern states but epidemics have not developed in the communities where these bacteria were found. Because of the need for further data bearing on the latter point and the availability of clinical material, during the early winter of 1945 to 1946 a series of diphtheria patients at the Charity Hospital, New Orleans, La., were studied in collaboration with Dr. Kay Kohara.

The seriousness of the disease varied from mild (eight cases), moderately severe (eight cases) and very severe (six cases) to fatal (two cases). No gravis strain was recovered from any of these patients. From eighteen patients, chiefly those with diphtheria of moderate or considerable severity and including one of the fatal cases, typical mitis strains were obtained while from the remaining six patients, with mild, severe or fatal disease, strains differing from mitis but not identical with the intermedius variety were isolated. Of the twenty-four strains of toxigenic diphtheria bacilli three proved capable of fermenting sucrose; use of this fer-

mentation reaction as a test for differentiating *C. diphtheriae* from non-pathogenic diphtheroid bacilli is thus undependable.

FIELD SPREAD PHENOMENA RELATED TO ELECTRICAL STIMULATION OF THE LATERAL OLFACTORY TRACT IN THE CAT.
James W. Ward, M.D. From The Department of Anatomy, Vanderbilt University School of Medicine, Nashville, Tenn.

Using a unipolar recording method a positive wave ($\frac{1}{50}$ sec. long) was picked up from all parts of the brain substance and the overlying bone and muscles. This activity resulted from electrical stimulation of the olfactory brain from the bulb back through the lateral olfactory tract to the region of the amygdaloid nuclei as far back as the optic chiasma. Direct nerve conduction was demonstrated from the bulb back to this anterior region of the piriform lobe. The positive wave appears to be a field spread current from the posterior region from which it can be elicited because: (1) it was not recorded with closely spaced bipolar leads unless they were in the "center" of origin, (2) no difference in latency of the response was noted with rapid sweeps on the C.R.O. no matter in what part of the head the unipolar pickup lead was located, (3) the response was not lost anywhere in or on the surface of the brain after a mid-sagittal section of the brain from the front backward to the level of the pons, nor was it affected by an additional hemisection of the brain behind the optic chiasma on the side which was stimulated. Section of the brain in the region of the lateral olfactory tract behind the stimulation electrode abolished the response. This response was negative when the recording lead was on the under surface of the brain below the region of distribution of the lateral olfactory tract (results comparable to those of Fox, McKinley and Magoun, 1944). The response is discussed in relation to a possible relationship with the E.E.G. under certain conditions.

FACTORS INFLUENCING CONTRACTILE FORCE OF THE HEART. *R. P. Walton, M.D., H. H. Brill, M.D., and M. DeV. Cotten, M.D.* (Introduced by *Harold Green, M.D.*) From The Department of Pharmacology, Medical College of South Carolina, Charleston, S. C.

The contractile force of a section of the right ventricle has been determined directly by introducing varying spring tensions into the classic Cushny heart lever system typically attached in the open-chest dog preparation. Changes in heart size are compensated for by mechanical adjustment or by a preliminary calibration procedure. Various maneuvers were conducted under relatively standardized conditions. Application of measured degrees of stretch to muscle section progressively increased the contractile force (isometric systolic tension) in extreme instances up to 600 per cent of that in the control period. Coronary ligation markedly decreased contractile force. Stenosis of the inferior vena cava, venous hemorrhage and arterial hemorrhage did not greatly affect contractile force until after substantial decrease in systemic arterial pressure. Saline infusions at the rate of 10 cc./Kg. over the period of about two minutes consistently raised venous pressures about 15 mm. with only insignificant effects on contractile force. (The same infusion rate in the intact animal markedly raises venous pressure.) Infusions at the rate of 20 to 40 cc./Kg. during the same period raised venous pressures 30 to 65 mm. with only limited or moderate effects on contractile force. Cardiotonic drugs (sympathomimetic group, veratrine and cardiac glycosides) moderately elevate venous pressure when they produce increases in contractile force. Metrazol, presumably without direct cardiac effects, increased contractile force 20 to 30 per cent under hypotensive conditions when there were substantial increases in the arterial pressure following the injection.

In summary, under these experimental conditions, contractile force is greatly increased by mechanical stretching but is only nominally affected by the degree of pressure changes occurring through ordinary variations in venous flow. When there is a serious degree of hypotension, an increase in arterial pressure increases contractile force possibly through an increase in coronary flow.

AMINOPTERIN THERAPY IN ACUTE LEUKEMIA. *Roy R. Kracke, M.D. and (by invitation) William H. Rise, Jr., M.D.* From The Department of Medicine, Medical College of Alabama, Birmingham, Ala.

Farber and associates recently reported that temporary remissions in acute leukemia in

children could be produced by certain folic acid antagonists. Since their original report, aminopterin (4-aminopterolyglutamic acid) has been used in the treatment of acute leukemia in twenty-two children and five adults in our clinic. Of the twenty-seven patients treated twelve are living and fifteen are dead. Aminopterin produced temporary clinical remissions in five of the living patients and significant temporary hematologic changes in others in the series. Those who experienced temporary remissions had no clinical symptoms and their blood and bone marrow appeared normal. The response was not consistent in all cases.

Toxic manifestations of aminopterin are: anorexia, ulcerations of the buccal mucosa,

glossitis, stomatitis, diarrhea, ulceration of the gastrointestinal mucosa and aplasia of the bone marrow. Toxic manifestations usually clear up four to five days after discontinuance of therapy. Aminopterin can be started again in small doses and increased to tolerance or until the desired effect is obtained.

The patients in our study can be classified into three groups: (1) Those in whom aminopterin had no appreciable effect, (2) those whose leukemia was apparently controlled temporarily but blood and bone marrow remained abnormal and (3) those experiencing temporary clinical remissions with absence of symptoms and a normal-appearing blood and bone marrow pattern.

Case Reports

Thyrotoxicosis Simulating Hyperparathyroidism*

MALCOLM M. STANLEY, M.D. and JOSEPH FAZEKAS, M.D.

Boston, Massachusetts

Washington, D.C.

WHEN a patient complains of typical symptoms and exhibits characteristic signs, the diagnosis of thyrotoxicosis is easily made. In some instances, however, many of these symptoms are lacking and the diagnosis is difficult. In such cases it is often necessary to obtain assistance from special laboratory procedures. Recently it has been found that determination of the accumulation of radioactive iodide by the thyroid gland is useful in diagnosis of thyrotoxicosis.¹³

The present report concerns a patient with thyrotoxicosis whose disease was obscured by the absence of many characteristic features and by the presence of azotemia, hypercalcemia and a normal heart rate. The greatly increased uptake of radio-iodide pointed to the diagnosis which, however, was established definitely only after repeated studies before and after treatment with antithyroid drugs.

CASE REPORT

L. D., a forty-four year old male clerk, entered the Pratt Diagnostic Hospital on June 9, 1947, because of vomiting, weakness, weight loss and nervousness. He was well until four months before when his muscles became stiff, lame and weak. He "felt shaky inside." Several days later his ankles became swollen. The stiffness of the muscles was pronounced for approximately two weeks and never completely left him. There was some intolerance to heat, in that he became uncomfortable with the usual bedclothing. He believed that his urine was darker than normal. Nocturia which had been present for years continued unchanged until admission. The bowel habits were normal, there was no diarrhea

and the stools were constantly brown. Two weeks after the onset of his illness the first attack of vomiting occurred. There was no abdominal pain or distention, "just a feeling of uneasiness over my stomach," and for several days he was unable to retain solids or liquids. Before the first admission there were five such episodes of vomiting, each lasting for three to seven days. He was, therefore, unable to eat normally and in four months lost approximately 50 pounds. He became progressively weaker, nervous and shaky and noted palpitation, dyspnea and exhaustion on slight exertion.

He had been hospitalized elsewhere on three occasions because of these complaints. Laboratory studies had included urinary specific gravities of 1.026 (February 25, 1947), 1.025 (March 14, 1947) and 1.015 (May 6, 1947). The last two urinalyses also had revealed 1+ albumin and a few granular casts. Examinations of the gastrointestinal tract, gallbladder and liver had shown no abnormalities.

Upon physical examination it was seen that the patient was quite ill, debilitated and cachectic but well oriented. The skin was pale, tanned, warm and dry; the palms were hot and dry. The eyeballs appeared to be sunken. The thyroid was smooth, firm and slightly enlarged but there was no bruit or thrill. The heart was normal in size, the beat was forceful and a grade II systolic murmur was heard over the precordium. The heart rate was 88 per minute. There was some muscle tenderness over the left arm and forearm and a rather coarse tremor of the fingers was present. The remainder of the physical examination revealed no abnormalities.

Laboratory data revealed that the urine was free of sugar and tests for albumin were 1+ to 2+. A few white cells, red cells and occasional hyaline and granular casts were noted. The

* From the Joseph H. Pratt Diagnostic Hospital and the Department of Medicine, Tufts College Medical School, Boston, Mass.

specific gravity on three examinations was 1.009, 1.010 and 1.012. After withholding fluids for sixteen hours the specific gravity was 1.013 on one occasion. A value of 1.013 was obtained after 1 cc. pitressin. The urinary phenolsulfonphthalein excretion was 15 per cent in fifteen

Gm. of globulin. The serum alkaline phosphatase was 3.4 Bodansky units per 100 cc. The blood carbon dioxide capacity was 69 volumes per cent. The blood non-protein nitrogen was 49 mg. per 100 cc. on two occasions.

X-rays showed the bones of the hands, skull,

TABLE I
SUMMARY OF PERTINENT DATA BEFORE AND DURING THE COURSE OF TREATMENT

Date	Calcium Intake (Gm./day)	Urinary Calcium (Gm./day)	Urinary Inorganic Phosphorus (Gm./day)	Serum Calcium (mg. %)	Serum Phosphorus (mg. %)	Serum Cholesterol (mg. %)	Blood NPN (mg. %)	Urine (specific gravity)	Basal Metabolic Rate	Weight (pounds)	Pulse	Treatment
6/10/47	144	..	1.009	+27, +24	111.5	88	Mercaptoimidazole 60 mg./day
6/11/47	49	1.013	+17, +22	
6/16/47	13.7	4.2	...	49	1.010 1.013 with pitressin	106	76	
6/17/47	+30, +31	72	Propylthiouracil 300 mg./day
6/21/47	.505	72	
6/22/47	.404	72	
6/23/47	.210	13.1	4.2	154	105	72	
6/24/47	.046	1.011	+29, +15	103.5	72	
6/25/47	.213	.525	.286	1.010	104	72	
6/26/47	.318	.900	.480	1.008	104	72	
6/27/47	.283	.481	.226	72	
6/28/47	.269	.638	.270	104	72	
6/29/47	.287	.460	.214	105	60	
6/30/47	.285	.526	.495	13.1	3.8	181	35	+4, +8	106	60	
7/1/47	.182	.163	
8/4/47	10.3	3.0	254	29	1.009 to 1.014 (1.021 with pitressin)	-13, -13	120.5	40	Propylthiouracil 300 mg./day
8/7/47043	29	-11, -8	45	Propylthiouracil 300 mg./day
10/10/47	10.3	3.8	183	..	1.009	138	45	
12/13/47	More than 2.5 Gm. daily for eight days preceding this visit	.026	10.4	3.8	160	..	1.020 (16-hour fast) 1.027 (two hours after 1 cc. pitressin)	146.5	45	Propylthiouracil 150 mg./day

minutes and 50 per cent in two hours. The urine was repeatedly sterile. The Sulkowitch test for increased urinary calcium was strongly positive. Several basal metabolic rates ranged from +17 per cent to +31 per cent.

Blood examination revealed a hemoglobin of 58 per cent (9.1 Gm. per cent) and hematocrit of 32 per cent. The white blood count was 5,700 per cu. mm., with polymorphonuclear leukocytes, 81 per cent; lymphocytes, 13 per cent; monocytes, 6 per cent. The blood sedimentation rate was 37/mm. in one hour by the Westergren method.

The serum sodium was 146 mEq./L., chloride, 100 mEq./L. The serum proteins totaled 7.0 G. per 100 cc., with 4.7 Gm. of albumin and 2.3

thorax, vertebrae and lower extremities to be normal. X-rays of the chest and gastrointestinal tract were normal. There was no calcification in the regions of the kidneys or adrenals. The electrocardiogram was within normal limits. Slit lamp examination revealed no band keratitis or abnormalities of the conjunctivae. Other laboratory data are shown in Table I.

On the second day the uptake by the thyroid of radioactive iodide was determined. A maximal accumulation of five to six times normal was found, indicating a hyperfunctioning gland.

Examples of the tests with I^{131} performed on two normal individuals and on the patient described in this report are shown in Figure 1.

The diagnosis of hyperthyroidism was sug-

gested by the weight loss, asthenia, forceful heart beat and the rapid uptake of radioactive iodide by the thyroid gland. Treatment with 2-mercaptoimidazole, 20 mg. every eight hours, was begun on the second hospital day.

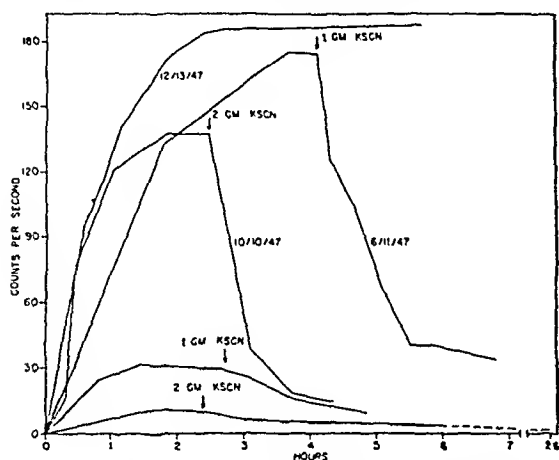


FIG. 1. The iodide accumulation by the thyroid gland in two normal subjects (curves without dates) and in the patient described in this report at the dates indicated. One to two hours before each test, virtually complete inhibition of organic binding of iodine in the thyroid gland was accomplished by administration of 100 mg. of mercaptoimidazole. One hundred microcuries of carrier-free I^{131} were given by mouth in each instance. Serial counts were made by means of a Geiger-Muller counter placed in contact with the skin over the thyroid isthmus. In normal subjects the collection of iodide by the thyroid was relatively slow, with maxima of 35 counts per second or less. The discharge after potassium thiocyanate was also gradual. On the other hand, in the patient the accumulation at the first test (6/11/47) was rapid, with a maximal count of five to six times normal. The loss of iodide after thiocyanate was also abrupt, even more rapid than the uptake. After four months of treatment the maximal count had decreased somewhat. After six months of treatment (12/13/47) the maximal accumulation was slightly higher than originally. This and the thyroid enlargement were presumably reflections of the stimulation of the thyroid by the increased thyrotropin secretion which occurred with the onset of hypothyroidism. The goiter which developed at this time was also probably the result of the same process. Subsequent similar tests were made under these conditions. Almost simultaneously the I^{131} content of the thyroid was determined in absolute terms by means of a sensitive gamma tube 35 cm. from the skin. Comparisons showed that in this patient 1 microcurie I^{131} (1 per cent) in the thyroid was equivalent to $5\frac{1}{2}$ counts per second obtained by counting with the older tube in contact with the skin.

In view of the high serum calcium and the strongly positive Sulkowitch test a low calcium diet was instituted, and the daily urinary excretion of calcium and inorganic phosphorus was

followed. Table 1 presents these values. Despite the low calcium intake the serum calcium remained elevated and the urinary excretion of calcium was high. During this same period the specific gravity of the urine was low, 1.008 to 1.012. At the time when this test period was completed, June 30th, the basal metabolic rate had returned nearly to normal, +4 to +8.

When the patient returned home after twenty-one days in the hospital, his general condition was only slightly improved. The vomiting continued during the first part of his hospital stay so that fluids were administered intravenously on several occasions. He weighed 6 pounds less than on admission; his pulse was slightly decreased from 76 per minute at the beginning of treatment to 60 on discharge. He was placed on a high caloric diet low in calcium and instructed to take propylthiouracil, 100 mg. every eight hours.

The patient was admitted for a second time during August 4-7, 1947. He had noted a marked improvement in his general health during the month since discharge. His strength and appetite had improved and there was no excessive fatigue. He had gained $14\frac{1}{2}$ pounds and was less pale and nervous. He had adhered closely to the low calcium diet and taken propylthiouracil 300 mg. daily. The nocturia had continued however. He had returned to his work on a part-time basis.

Upon physical examination, with the exception of a pulse rate of 40 per minute, there were no abnormalities noted. The thyroid was not palpable.

The blood non-protein nitrogen was 29 mg. per cent; the serum cholesterol was 254 mg. per cent. Urinary phenolsulfonphthalein excretion was 15 per cent in fifteen minutes and 48 per cent in sixty minutes. The total serum proteins were 6.2 Gm. per cent, with albumin 4.3 and globulin 1.9. The hemoglobin was 65 per cent (10.2 Gm. per cent), with a color index of 0.98. The white blood count was 4,300, with polymorphonuclears 45 per cent; lymphocytes, 43 per cent; monocytes, 7 per cent; eosinophiles, 3 per cent; basophiles, 2 per cent. The basal metabolic rates ranged from -8 to -13. The electrocardiogram revealed a sinus bradycardia.

The marked improvement in symptoms, the rise in blood cholesterol and the normal basal metabolic rate were evidence of abatement of hyperthyroidism. The blood non-protein nitrogen and serum calcium had also returned to

normal. The low calcium diet was discontinued and the patient was advised to continue taking propylthiouracil, 100 mg. every eight hours.

The patient was again seen on October 10, 1947. He was asymptomatic at that time except for nocturia, once nightly, which had been noted about half the time. His weight was then 138 pounds, a total gain of 34.5 pounds. He had resumed a normal diet and continued to take propylthiouracil, 300 mg. daily.

Physical examination revealed no abnormalities except a pulse rate of 45 per minute and a slightly enlarged thyroid gland. Laboratory studies revealed a normal urine, with a specific gravity of 1.009 in a random specimen. The blood picture had returned to normal. Additional data are shown in Table 1 and Figure 1.

At the last visit, December 13, 1947, he weighed 146.5 pounds which was normal for him. He had taken 300 mg. of propylthiouracil daily as before. He had recently noted increased sensitivity to cold and increasing tightness of his shirt collars. During the eight days before this visit he had taken 2 quarts of milk daily in addition to his regular diet. On this regimen the nocturia, which had almost completely disappeared, returned with a frequency of about once every other night.

On examination the pulse was 46 per minute. The eyes were slightly puffy and the voice hoarse. The thyroid was moderately enlarged but no bruit or thrill was detectable. The urine was normal and the specific gravity was 1.020 after a fast of sixteen hours. Two hours after 1 cc. pitressin the specific gravity was 1.027. An intravenous pyelogram was entirely normal. Because of the presence of hypothyroidism, the patient was instructed to reduce the dose of propylthiouracil to 150 mg. daily.

COMMENTS

Although the weight loss, muscular weakness, nervousness, palpitation, the forceful heart beat, the elevated basal metabolic rate and lowered serum cholesterol were suggestive of thyrotoxicosis, there were many features against this diagnosis. The weight loss could have been explained by the decreased food intake resulting from repeated vomiting. A low serum cholesterol would be expected with cachexia, particularly in the presence of moderate anemia.

The pulse rate which ranged from 70 to 80 per minute seemed quite unusual in the presence of thyrotoxicosis. However, the statement of the patient that he had always had a slow pulse while in good health was substantiated when it was found to be 45 per minute after two months of treatment. The rate of 70 to 80 per minute therefore represented tachycardia for him.

Recent studies^{1,11-13,15} have shown that hyperplasia of the thyroid is accompanied by an increased collection of radioactive iodide by the gland. In thyrotoxicosis, the most frequent concomitant of hyperplasia, there is a rapid uptake of iodide by the gland, with maximal accumulations above 60 counts per second. Often levels of several times this figure are attained as in the case reported herein. The rate of discharge of the iodide by thiocyanate is comparable to the speed of accumulation. In normal subjects the rate of uptake is slow, with maxima of 35 counts per second or less. The rate of loss of iodide from the gland under the influence of thiocyanate is also gradual and is similar to the collection.

The marked increase over normal in the accumulation of radioactive iodide by the thyroid added strong support to the diagnosis of thyrotoxicosis. It was because of this that proper treatment was instituted promptly in spite of evidence which seemed to make this diagnosis untenable. The subsequent course with antithyroid therapy leaves little doubt that thyrotoxicosis was the primary abnormality although it is probable that it was not the only disease.

The repeated episodes of vomiting, muscular weakness, hypercalcemia, azotemia, impairment of kidney function and increased excretion of calcium in the urine which continued for a time after institution of a low calcium intake at first made the diagnosis of hyperparathyroidism tenable. The normal serum alkaline phosphatase was not considered unusual in the absence of bone changes and also the serum phosphorus was normal. The reversion to normal of the high serum calcium and the dramatic improvement in the other symptoms while

under antithyroid treatment made it improbable that this disease was present.

Addison's disease was also suggested by the vomiting, weakness, tanned skin, weight loss, hypotension, azotemia and fixed urinary specific gravity. The normal-sized heart with a forceful beat, the warm skin and the elevated basal metabolic rate were against this diagnosis. The pigmentation of the skin could be adequately explained by recent exposure to the sun; there was no pigmentation of the mucous membranes. The levels of sodium, potassium and chloride in the serum were normal. The lasting improvement without specific therapy for Addison's disease excluded this disorder. The changes in calcium metabolism could not be explained on the basis of adrenal cortical hypofunction.

By calculation from the food history the intake of calcium, which had approximated 1.4 Gm. per day prior to the first admission, was higher than average. It was suggested that the whole picture might be explained on this basis, with the hypercalcemia resulting from the inability of the kidneys to excrete the excess calcium adequately. The presence of kidney disease, either chronic glomerulo- or pyelonephritis, was postulated. However, the calcium intake was not greatly in excess of that taken by many individuals. There were no corneal or conjunctival lesions such as have been described in individuals with hypercalcemia of long duration.¹⁶ If the syndrome were on this basis, it would be expected that the change to a low intake would result in a significant decrease in the serum calcium or in the urinary calcium excretion. This did not occur in nine days. (Table 1.) Instead, however, the change to normal values occurred over a period of several weeks. This interval would probably be required for the reversion of such metabolic disturbances due to thyrotoxicosis even under adequate treatment with an antithyroid drug.

The evidence for renal disease consisted of isosthenuria, impaired urinary excretion of phenolsulfonphthalein, slight azotemia

and moderate anemia. The urine was sterile, contained slight to moderate amounts of albumin, a few white and red blood cells and occasional hyaline and granular casts. Improvement with treatment was accompanied by return to normal of the blood non-protein nitrogen and an increased ability of the kidneys to concentrate the urine. The type of renal disturbance is not known. The presence of kidney dysfunction following acute alkalosis was considered; the only evidence for this latter was a plasma carbon dioxide capacity of 69 volumes per cent. In the absence of a history of ingestion of alkalis the repeated vomiting, with perhaps accompanying dehydration, remained a possible etiologic factor; the normal plasma chlorides made this unlikely. However, since both the acute alkalosis and renal damage may be transient and reversible, it is possible that the former may have been present in our patient before admission. He had no evidence of residual kidney disease after recovery from thyrotoxicosis.

Other common causes of hypercalcemia were not present. The patient had not received medication containing vitamin D so the intake of this substance was not excessive. The serum proteins were normal. The four normal subjects studied by Dietrick, Whedon and Shorr⁴ exhibited increased urinary and fecal calcium excretion during six to seven-week periods of complete immobilization produced by plaster casts extending from the umbilicus to the toes. Slight elevation of the serum calcium levels occurred during the latter part of the period of immobilization and early in the recovery phase, with a maximum rise of 1.8 mg. per cent. The patient described herein was never confined to bed for longer than one or two days at a time and never without bathroom privileges; his activity was not restricted during recumbency. Thus it seemed unlikely that bed rest was an important factor in bringing about the changes in calcium metabolism in our patient.

The vomiting, which was such a prominent symptom, was probably the result of

the elevation of serum calcium. Although an increased urinary and fecal excretion of calcium occurs frequently in thyrotoxicosis,^{2,9} hypercalcemia is uncommon. In the great majority of cases of thyrotoxicosis the levels of calcium in the serum are normal. However, in the review of Puppel et al.⁹ cases were cited with serum calcium levels of 12.1 mg. per cent (E. M.), 12.4 mg. per cent (M. C.) and 14 mg. per cent (L. M.) while on low calcium intakes. On the other hand, Robertson¹⁰ considered the average levels of 9.71 mg. per cent (range 9.1 to 10.8) in the group of fourteen thyrotoxic patients studied by him to be significantly lower than the average of 10.39 mg. per cent for normal persons (range 9.9 to 11.1).

As further evidence for frequent disturbances in calcium metabolism in thyrotoxicosis, Golden and Abbott⁵ found roentgenologic evidence of significant osteoporosis in 22 per cent of 110 cases. Since only chest films were available in sixty-three instances, the true incidence was probably higher than this. (Of nine patients in whom complete studies were available six had decalcification.) The x-ray picture of metastatic cancer and what was clinically termed "arthritis" have been described with osteoporosis due to thyrotoxicosis.^{8,9} Several instances of spontaneous fractures due to such osteoporosis have been reported.^{3,6,14} The skeletal system of the patient described here appeared to be normal by x-ray.

Although at times there may be a resemblance between the clinical picture due to thyrotoxicosis and to hyperparathyroidism, they are usually easily distinguishable. Six instances of the simultaneous occurrence of these two diseases in the same person, three of which were confirmed at operation, have been reviewed by Miller and Evans.⁷

In our patient, because of the hypercalcemia and associated renal dysfunction, the diagnosis of co-existing hyperparathyroidism could not be lightly dismissed even with the normal serum phosphorus and alkaline phosphatase levels. After com-

plete response to antithyroid medication, however, it could be ruled out with certainty.

In the usual case of thyrotoxicosis the kidneys are able to excrete the increased amounts of calcium and to maintain a normal serum calcium. In our patient an explanation of the situation might be that the kidneys, while able to excrete more than normal amounts, because of impaired function could not clear enough calcium to prevent hypercalcemia. This, of course, presumes that the primary event was an increased mobilization of calcium from the bones as a result of the excessive catabolism generally occurring in thyrotoxicosis.² This explanation would not be compatible with other theories as to the cause of the excessive excretion of calcium in this disease.

SUMMARY

A patient with thyrotoxicosis exhibited recurrent vomiting, a normal heart rate, azotemia, a fixed urinary specific gravity and hypercalcemia with increased calcium excretion in the urine. Strong evidence for the correct diagnosis was provided by the elevated uptake of radioactive iodide by the thyroid gland. While under treatment with antithyroid drugs alone, he attained a state of normal health, including normal kidney function. The correction of the abnormalities while under specific therapy for thyrotoxicosis made it unlikely that hyperparathyroidism co-existed and thus confirmed the original diagnosis.

Acknowledgment: We are grateful to Dr. E. B. Astwood for helpful suggestions in the preparation of this manuscript.

ADDENDUM

Since this manuscript was submitted, further information has become available. At the patient's last visit, November 24, 1948, three months after all antithyroid medication had been discontinued, he was asymptomatic. He weighed 170 pounds. The thyroid was barely palpable. The heart rate was 45 beats per minute. There were no other physical abnormalities. The urine was normal, with a specific gravity of 1.016

in the random specimen. The serum calcium was 10.2 mg. per cent, phosphorus 3.2 mg. per cent, cholesterol 178 mg. per cent and alkaline phosphatase 1.8 Bodansky units per 100 cc. The thyroid radioactive iodine uptake was 14.3 counts per second, or 2.6 per cent, values which were within normal limits.

REFERENCES

1. ASTWOOD, E. B. and STANLEY, M. M. Use of radioactive iodine in the study of thyroid function in man. *West. J. Surg.*, 55: 625, 1947.
2. AUB, J. C., BAUER, W., HEATH, C. and ROPES, M. Studies of calcium and phosphorus metabolism. III. The effects of thyroid hormone and thyroid disease. *J. Clin. Investigation*, 7: 97, 1929.
3. BARTELS, E. C. and HACCART, G. E. Osteoporosis in hyperthyroidism; reports of two cases with compression fracture of vertebrae. *New England J. Med.*, 219: 373, 1938.
4. DIETRICK, J. E., WHEDON, G. D. and SHORR, E. Effects of immobilization upon various metabolic and physiologic functions of normal men. *Am. J. Med.*, 4: 3, 1948.
5. GOLDEN, R. and ABBOTT, H. Relation of thyroid, adrenals, and islands of Langerhans to malacic diseases of bone. *Am. J. Roentgenol.*, 30: 641, 1933.
6. MEANS, J. H., HERTZ, S. and LERMAN, J. Nutritional factors in Graves' disease. *Ann. Int. Med.*, 11: 429, 1937.
7. MILLER, E. S. and EVANS, L. R. Simultaneous hyperfunction of the thyroid and parathyroid glands. *New England J. Med.*, 227: 949, 1942.
8. PLUMMER, W. A., DUNLAP, H. F. and MOORE, A. B. Three cases of thyrotoxicosis with osteoporosis. *Proc. Staff Meet., Mayo Clin.*, 3: 119, 1928.
9. PUPPEL, I. D., GROSS, H. T., MCCORMICK, E. K. and HERDLE, E. The rationale of calcium, phosphorus, and vitamin D therapy in clinical hyperthyroidism. *Surg., Gynec. & Obst.*, 81: 243, 1945.
10. ROBERTSON, J. D. Calcium and phosphorus excretion in thyrotoxicosis and myxedema. *Lancet*, 242: 672, 1942.
11. STANLEY, M. M. The use of radioactive iodine in the study of normal and abnormal thyroid function. *Bull. New England M. Center*, 10: 28, 1948.
12. STANLEY, M. M. and ASTWOOD, E. B. Determination of the relative activities of antithyroid compounds in man using radioactive iodine. *Endocrinology*, 41: 66, 1947.
13. STANLEY, M. M. and ASTWOOD, E. B. The accumulation of radioactive iodide by the thyroid gland in normal and thyrotoxic subjects and the effect of thiocyanate on its discharge. *Endocrinology*, 42: 107, 1948.
14. THOMPSON, W. O. Symposium on surgical lesions of thyroid; diagnosis of thyrotoxicosis. *Surgery*, 16: 647, 1944.
15. VANDERLAAN, J. E. and VANDERLAAN, W. P. The iodide-concentrating mechanism of the rat thyroid and its inhibition by thiocyanate. *Endocrinology*, 40: 403, 1947.
16. WALSH, F. B. and HOWARD, J. E. Conjunctival and corneal lesions in hypercalcemia. *J. Clin. Endocrinology*, 7: 644, 1947.

Influenzal Meningitis in Adults*

Report of a Case Complicating the Nephrotic Syndrome

MARVIN C. BECKER, M.D. and CLIFFORD L. SPINGARN, M.D.

New York, New York

ALTHOUGH *Hemophilus influenzae* is a common cause of acute, purulent meningitis in children, this type of meningeal infection has rarely been encountered in adults. A review of the literature revealed only thirty reports dealing with this disease in persons twenty or more years of age. Analysis of the reports indicated that the disease in the older age groups differed in some respects from that in the very young. It seemed of interest, therefore, to report the following case of *Hemophilus influenzae*, type B, meningitis occurring in a woman of forty-eight and to emphasize some of the characteristics of the infection. A unique feature of the case is the fact that the meningitis occurred as a complication of the nephrotic syndrome.

CASE REPORT

A forty-eight year old, white female school teacher complaining of left anterior chest pain of two days' duration was admitted to The Mount Sinai Hospital, New York, on October 25, 1947.

Two weeks before admission she developed a severe upper respiratory infection, associated with a low grade fever and a dry cough. The fever subsided in a few days but the cough persisted and with the onset of the chest pain it became productive of rusty sputum and there was a temperature elevation to 101°F. (rectally).

Four months prior to the onset of her present illness she developed bilateral pitting edema of the legs. The blood pressure was 120/80. Urinalysis at that time showed 4 plus albuminuria with many hyaline casts. The serum protein level was 3.6 Gm. per cent and the serum cholesterol was 318 mg. per cent. On the basis of these findings a diagnosis of the nephrotic stage of chronic glomerulonephritis was made.

She was placed on a high protein, low salt diet and was given thyroid extract (1 gr. three times daily), vitamin B complex and ammonium chloride (2 Gm. three times daily). On this regimen she felt well and had only minimal edema of the legs. The albuminuria persisted without change.

On admission to the hospital examination revealed a well nourished, well developed, acutely ill, white female of forty-eight, with marked respiratory distress. The rectal temperature was 101°F., pulse rate was 100 and the respiratory rate was 32. There was a well marked arcus senilis and the pupils were contracted. The neck veins were distended. There was some splinting of the left thoracic cage. The percussion note was impaired over the left chest posteriorly and in the left axilla. Bronchial breathing was heard over the left lower lobe and there was a grating friction rub in the left axilla. There were fine, moist inspiratory rales at the base of the left lung. The heart sounds were good; a soft systolic murmur was heard only at the apex. The blood pressure was 108/70. The abdomen was slightly distended. The liver, spleen and kidneys were not felt. There were no abnormalities on rectal or vaginal examination. Examination of the extremities revealed mild edema of both ankles. The reflexes were normal.

The specific gravity of the urine was 1.012. It contained no sugar but there was a large amount of albumin present, with many waxy, hyaline and granular casts and two or three white blood cells as well as two or three red blood cells per high power field. The hemoglobin concentration of the blood was 9.6 Gm.; the red blood cell count was 3.39 million; the white blood cell count was 9,350 with 2 per cent myelocytes, 65 per cent non-segmented polymorphonuclear neutrophils, 14 per cent segmented polymorphonuclear neutrophils, 16 per cent lymphocytes and 3 per cent monocytes.

* From The Mount Sinai Hospital, New York, N. Y.

The erythrocyte sedimentation rate was 135 mm. in one hour (Westergren). The blood urea nitrogen was 7 mg. per cent.

A typing of the sputum for pneumococci was negative. Sputum culture revealed *Streptococcus viridans* (alpha) and *Streptococcus anhemolyticus* (gamma). Roentgen examination of the chest at the bedside showed pneumonic infiltrations occupying most of the left lung. The provisional diagnosis was severe lobar pneumonia with the nephrotic syndrome.

The patient was given injections of crystalline penicillin G (100,000 units every three hours) intramuscularly. During the first twenty-four hours she became markedly stuporous and her temperature rose to 103.2°F. The pulse was 128 and the respiration was 36. She was given a 500 cc. blood transfusion and the penicillin was increased to 200,000 units every three hours. Despite these measures the stupor continued. The picture was interpreted as one of profound toxemia due to an overwhelming infection in a nephrotic subject.

On the third hospital day improvement was noted. The patient was now rational and cooperative. Her rectal temperature had dropped to 100°F. There were no meningeal signs. Another blood transfusion was administered and, in addition, she was given amigen solution intravenously (1,000 cc.) in an attempt to combat hypo-amino-acidemia. Although the organisms causing the infection were still unknown, it was believed that there had been a favorable response to therapy. That evening, however, her condition became worse. Her temperature rose to 104°F., with a pulse rate of only 66. The blood pressure was now 170/70. The patient appeared drowsy, complained of severe headache and vomited. Lumbar puncture revealed cloudy spinal fluid containing 2,200 cells per cu. mm., with a predominance of polymorphonuclear leukocytes. The Pandy reaction was 4 plus. No organisms were seen on direct smear of the spinal fluid. Because of meningitis, the patient was given 4 Gm. of sodium sulfadiazine intravenously and this was followed by 1 Gm. every four hours intravenously. The dose of penicillin was increased to 400,000 units intramuscularly every two hours and 10,000 units of penicillin were given intrathecally.

On the fourth hospital day she relapsed into a semistupor. Examination of the ears, nose and throat for foci of primary infection revealed no active disease although the right antrum was

dark to transillumination. Later that day *H. influenzae*, type B, was identified in the blood culture taken on admission and was also found in a culture of the sputum and in the cerebrospinal fluid. Lumbar puncture was repeated and 100 mg. of streptomycin calcium chloride complex were injected intrathecally. In addition, 0.5 Gm. of streptomycin was given intramuscularly every six hours. At this time therapy consisted of sodium sulfadiazine intravenously, streptomycin intramuscularly and intrathecally and penicillin intramuscularly.

By the seventh day general improvement was clearly apparent. The patient became alert, responsive and completely rational. The neck signs were almost gone. She was able to take sulfadiazine and fluids by mouth. The spinal fluid culture was negative and concentration of the sugar had risen to 55 mg. per cent from 15 mg. per cent. Roentgen examination of the chest revealed fluid at the left base which partially obscured a pulmonary infiltration.

By the tenth day the temperature had fallen to 98.6°F. Use of sulfadiazine and penicillin was discontinued. Although the cough persisted, the pulmonary signs had definitely cleared. Spinal fluid glucose concentration was 70 mg. per cent. Blood urea nitrogen was 9 mg. per cent, cholesterol was 440 mg. per cent, total protein was 4.6 Gm. per cent, with albumin 2.7 Gm. per cent and globulin 1.9 Gm. per cent.

By the twelfth day she was out of bed in a chair and complained only of a slight headache. The signs in the chest had almost completely cleared but x-ray examination of the chest still revealed infiltration in the lower two-thirds of the left lung. On the fourteenth day streptomycin was discontinued.

The remainder of the hospital stay was uneventful. The patient complained of mild frontal headache from time to time but the temperature remained normal. On attempting to walk she was unsteady and staggered slightly. An otologic consultant was of the opinion that slight impairment of vestibular function was present. Analysis of the blood now revealed a total protein of 5.3 Gm. per cent, with albumin 2.9 Gm. per cent and globulin 2.4 Gm. per cent, cholesterol 500 mg. per cent, blood urea nitrogen 17 mg. per cent. Roentgen examination three weeks after admission still revealed some infiltration in the left lower lobe of the lung. This lobe was smaller than previously noted and its appearance suggested some degree of

atelectasis. The patient was discharged with no residual meningeal or pulmonary findings twenty-four days after admission.

COMMENT

Meningitis due to *H. influenzae* is essentially a disease of early childhood.

tributable to a humoral antibody. Moreover, they pointed out that between the ages of two months and three years this bactericidal power is almost completely lacking from the human blood and that after three years it increases, reaching its maximum in adults.

TABLE I
ESSENTIAL CLINICAL AND LABORATORY FINDINGS IN SIXTEEN CASES OF INFLUENZAL MENINGITIS IN ADULTS

Cases	Authors	Age	Sex	Type of Onset	Primary or Secondary	Cultures		Complications of Meningitis	Treatment	Outcome
						Spinal Fluid	Blood			
1	Cohoe ²	33	M	Head injury two weeks prior	?S	Smear and culture positive	Negative	None	Non-specific lumbar puncture	Recovery
2	Needles ³	29	M	Tooth extracted four days prior	?S	Culture positive	None	None	Non-specific	Recovery
3	Dyke ⁴	29	M	Ear infection preceding onset	S	Smear and culture positive	None	None	Non-specific	Recovery
4	Neal et al. ⁵	28	M	Six-day history of headache and vomiting	P	Smear and culture positive	Negative	Deafness	Antimeningeal and antiinfluenzal serum	Recovery
5	Neal et al. ⁵	38	M	Followed severe head injury	S	Culture positive	None	None	Antimeningeal and antiinfluenzal serum	Recovery
6	Watson-Williams ¹⁴	46	F	Followed ear infection of seven days	S	Smear and culture positive	None	None	Non-specific intravenous silver	Recovery
7	Teggart ⁶	60	M	Two-week history of lethargy, headache, etc.	P	Culture negative; smear, small gram-negative bacteria	None	None	Soluseptasine	Recovery
8	Mulder ⁷	28	M	Tonsillitis for five days	S	Culture positive	None		Non-specific	Death
9	Pellegrini ⁸	58	M	Headache for five days	P	Smear and culture positive	None	None	Sulfonamides	Recovery
10	Neal et al. ⁹	51	M	Headache	P	Culture positive	Negative	None	Sulfapyridine, sulfanilamide, serum	Recovery
11	Neal et al. ⁹	35	M	Followed submucous resection and ethmoidectomy	S	Culture positive	Negative	None	Sulfapyridine, serum	Recovery
12	Neal et al. ⁹	22	M		P	Culture positive	Negative	None	Sulfapyridine, serum	Recovery
13	Harold ¹⁰	59	M	Three-day history of headache	P	Culture positive	None	None	Sulfapyridine	Recovery
14	Mutch ¹¹	30	M	Two-week history of headache	P	Culture negative; smear, gram-negative bacillus	None	None	Sulfonamides	Recovery
15	Baumgartner and Nuzum ¹⁵	39	F	Ear infection of one week	S	Culture positive	None	None	Sulfanilamide	Recovery
16	Becker and Spingarn	48	F	Upper respiratory infection, pneumonia, nephrotic syndrome	S	Culture positive	Positive	None	Penicillin, sulfadiazine, streptomycin	Recovery

Most of the cases occur during the first three years of life. The incidence drops sharply from the fourth to the tenth years and the disease is very infrequently seen after the age of twenty. The relation of age to the incidence of this infection has been of interest to immunologists. Fothergill and Wright¹ demonstrated that human blood was highly bactericidal for influenza bacilli and that the bactericidal power is at-

Since Cohoe's² first report of a case of *H. influenzae* meningitis in an adult, we were able to find reports of twenty-nine additional cases. The essential clinical features of fifteen of the cases that were reported in sufficient detail have been tabulated (Table 1) to indicate some of the characteristics of the disease in the adult.

Although in children influenzal meningitis occurs with equal frequency in both

males and females, in adults thirteen of the patients were males. This sex difference is probably a fortuitous one due to the small series. In children influenzal meningitis has been regarded generally as a primary infection.^{7,12,13} In the group of adults four were secondary to a severe upper respiratory infection such as acute tonsillitis or acute otitis media.^{4,7,14,15} One case occurred following a submucous resection and an ethmoidectomy.⁹ Two cases occurred after head injuries^{2,5} and one followed a tooth extraction.³ Only seven (46 per cent) of the cases were regarded as primary meningeal infections.^{5,6,8-11} In our case cultures of the sputum, blood and spinal fluid all yielded *H. influenzae*, type B. Apparently this is the first reported adult case in which meningitis followed primary pneumonia due to this organism.

In children influenzal meningitis has been attended by a case fatality rate of over 90 per cent. Since 1937, use of anti-influenzal serum, sulfonamides, penicillin and finally, streptomycin, singly and in combination, has reduced this to a low level.^{17,18} However, in the group of adult cases, among eight reported prior to 1940 and the patients treated with a variety of non-specific measures, there was only one death. There were no deaths in seven other patients whose cases were reported since 1940 who were treated with sulfonamides and serum. Neurologic complications due to residual damage to brain and cranial nerves were noted in only one patient⁵ although these have been common among children who survived the infection. These findings suggest that the prognosis of the disease in adults is better than in children.

The occurrence of the nephrotic syndrome complicated by *H. influenzae* pneumonia and meningitis in an adult has not been previously recorded. It is well known that nephrotic subjects are very susceptible to bacterial infections due to pneumococci and streptococci which may prove fatal. In fact, when our patient was first seen with pneumonia, a pneumococcal or streptococcal infection was diagnosed because

of the nephrotic background. Penicillin therapy was therefore instituted. The relationship of the nephrotic syndrome to the onset of the infection is one of some interest since the former state may have impaired the immunologic defense of the patient. In the nephrotic syndrome hypoproteinemia is associated with a definite decrease in the antistreptolysin titer in children.¹⁹ Although we have no evidence regarding the bactericidal power of the blood for influenza bacilli in adults with the nephrotic syndrome, it is possible that this was reduced or absent as it is in infants. Consequently, the nephrotic state may have been an important factor favoring the onset of meningitis at an age when the disease is uncommon.

SUMMARY

1. A case of *Hemophilus influenzae*, type B, meningitis and pneumonia complicating the nephrotic syndrome is reported in a woman of forty-eight.
2. The overwhelming infection responded promptly to use of intrathecal and intramuscular streptomycin in the usual therapeutic dosages.
3. A review of the literature pertaining to *H. influenzae* meningitis in adults revealed features which distinguish it from the disease as it occurs in infants and children.

REFERENCES

1. FOTHERGILL, L. D. and WRIGHT, J. Influenzal meningitis. The relation of age incidence to the bactericidal power of blood against the causal organism. *J. Immunol.*, 24: 273-285, 1933.
2. COHOE, B. A. Influenzal meningitis. *Am. J. M. Sc.*, 137: 74, 1909.
3. NEEDLES, W. Influenzal meningitis with recovery. *J. A. M. A.*, 99: 1342-1343, 1932.
4. DYKE, S. C. and LITTLE, C. J. H. Meningitis due to bacillus of the Pfeiffer type. *Lancet*, 226: 1392-1393, 1934.
5. NEAL, J. B., JACKSON, H. W. and APPLEBAUM, E. Meningitis due to the influenza bacillus of Pfeiffer. A study of 111 cases with 4 recoveries. *J. A. M. A.*, 102: 513-518, 1934.
6. TEGGART, B. Influenzal meningitis treated with soluseptasine and lumbar puncture. *Brit. M. J.*, 1: 1365, 1938.

7. MULDER, J. Hemophilus influenza of the respiratory type as a cause of purulent meningitis. *J. Path. & Bact.*, 48: 175-185, 1939.
8. PELLEGRINI, M. La meningite purulente de Pfeiffer nell' adulte. *Gior. d. med. prat.*, 21: 267-276, 1939.
9. NEAL, J. B., APPLEBAUM, E. and JACKSON, H. W. Sulfapyridine and its sodium salt in the treatment of meningitis due to pneumococcus and H. influenzae. *J. A. M. A.*, 115: 2055-2058, 1940.
10. HAROLD, J. T. Pfeiffer bacillus meningitis. Recovery with chemotherapy. *Lancet*, 2: 308-309, 1941.
11. MUTCH, N. Pfeiffer bacillus meningitis. *Lancet*, 2: 751-753, 1941.
12. PITMAN. Quoted by Mulder.
13. HUNTINGTON, R. W., JR. and WILKES-WEISS, D. Association of otitis media and pneumonia with the onset of influenza meningitis. *J. Pediat.*, 9: 456-461, 1936.
14. WATSON-WILLIAMS, E. Influenzal meningitis in an adult with recovery. *Lancet*, 233: 1430-1431, 1937.
15. BAUMGARTNER, M. M. and NUZUM, T. O. Influenzal meningitis treated with sulfanilamide and spinal drainage; recovery. *Wisconsin M. J.*, 40: 579, 1941.
16. TOPLEY and WILSON. Principles of Bacteriology and Immunology. 3rd ed. Revised by WILSON, G. S. and MILES, A. A. Baltimore, 1946. Williams & Wilkins Co.
17. ALEXANDER, H. E. and LEIDY, G. The present status of treatment for influenzal meningitis. *Am. J. Med.*, 2: 457-465, 1947.
18. ALEXANDER, H. E. Treatment of type B Hemophilus influenzae meningitis. *J. Pediat.*, 25: 114-126, 1944.
19. SEEGAL, D. In Columbia Combined Staff Conference on the nephrotic syndrome. *Am. J. Med.*, 2: 386-401, 1947.

Endocarditis Due to *Hemophilus Influenzae**

FREDERICK C. GOETZ, M.D., and EDWIN W. PETERSON, M.D.

Boston, Massachusetts

BACTERIAL endocarditis due to a gram-negative organism is relatively rare and involves therapeutic problems of considerable interest. Therefore, we are reporting two cases of *Hemophilus influenzae* endocarditis, both resulting in recovery. One of these patients was cured by streptomycin and it is probable that the recovery of the other is attributable to streptomycin.

CASE REPORTS

CASE I. (Fig. 1.) Mrs. E. B., (No. 558876) † a thirty-two year old housewife, entered the hospital on January 2, 1947, because of a nightly fever of two months' duration. At the age of five, twenty-seven years previously, she had had severe migrating polyarthritides, diagnosed as rheumatic fever, which had left her with a "bad heart." Her only symptom through the years, however, was slight dyspnea on exertion.

About fifteen months before entry she began to lose weight and a few months later her appetite failed. She had lost about 40 pounds at the time of admission. Two months before entry she developed a fever of 102°F. and thereafter every evening ran a temperature between 99 and 102°F. During the first febrile month she was given penicillin-in-oil injections daily for two weeks. During the second month she was given a second course of 2 injections daily for one week. This therapy had no effect on the fever and the patient finally sought hospitalization.

Physical examination revealed a poorly nourished young woman with petechiae visible in the conjunctivae and on the palate. The chest was clear. The heart was not enlarged and exhibited a normal rhythm at a rate of 80. There was a systolic thrill over the aortic area

and a diastolic thrill at the apex. Systolic and diastolic murmurs were audible at both the base and apex, consistent with mitral and aortic valvular disease. Blood pressure was 120/40-0. The spleen was palpable 1 cm. below the left costal margin and there was moderate clubbing of the fingers.

Laboratory data revealed the following: The white blood count averaged 7,000 cells per cu. mm., the differential count being normal; hemoglobin remained at about 10 Gm. per cent; the sedimentation rate was 1.4 mm. per minute. Repeated urinalyses were negative. X-ray of the chest showed some prominence of the left ventricle but was otherwise not remarkable. The electrocardiogram was normal.

During the hospital course the patient ran an oscillating fever, the temperature usually being normal in the morning and as high as 103.8°F. by late afternoon. After three weeks a definite bacteriologic diagnosis had not been made, despite venous blood cultures twice daily, an arterial blood culture and a sternal marrow culture. Nevertheless, it was decided to start the patient on penicillin, one million units daily by constant intramuscular drip, as a therapeutic trial. During the eight days in which the ineffectuality of this treatment became apparent, an organism was recovered from the previous blood cultures and identified as *H. influenzae*. It grew too slowly to allow determination of penicillin sensitivity but was inhibited by streptomycin in a concentration of 2 units (0.002 mg.) per cc. Consequently, penicillin was stopped and streptomycin was begun at a dosage of 0.4 Gm. every four hours, or 2.4 Gm. per day. Although the streptomycin serum level at this dosage was over 16 units per cc., there was not an immediate fall in temperature to normal and it was feared that the resistance of the organism to streptomycin was rapidly increasing. The dose was therefore increased on the fourth day to 0.7 Gm. every four hours, or 4.2 Gm. per day. This gave a serum level of over 32 units per cc., but the

† This case has previously been noted elsewhere as a progress report¹ and was also briefly mentioned by Paul, Bland and White.²

* From the Medical Services of the Massachusetts General Hospital, Boston, Mass.

temperature continued to swing as high as 101°F. On the eighth day of streptomycin therapy the temperature reached 103°F. and the patient developed a generalized, pruritic, erythematous rash. Benadryl and, subsequently, pyribenzamine were administered; with the

She is able to get along under most conditions, except when walking on an uneven surface in the dark.

Comment. This case represents one of the earlier successful attempts to cure

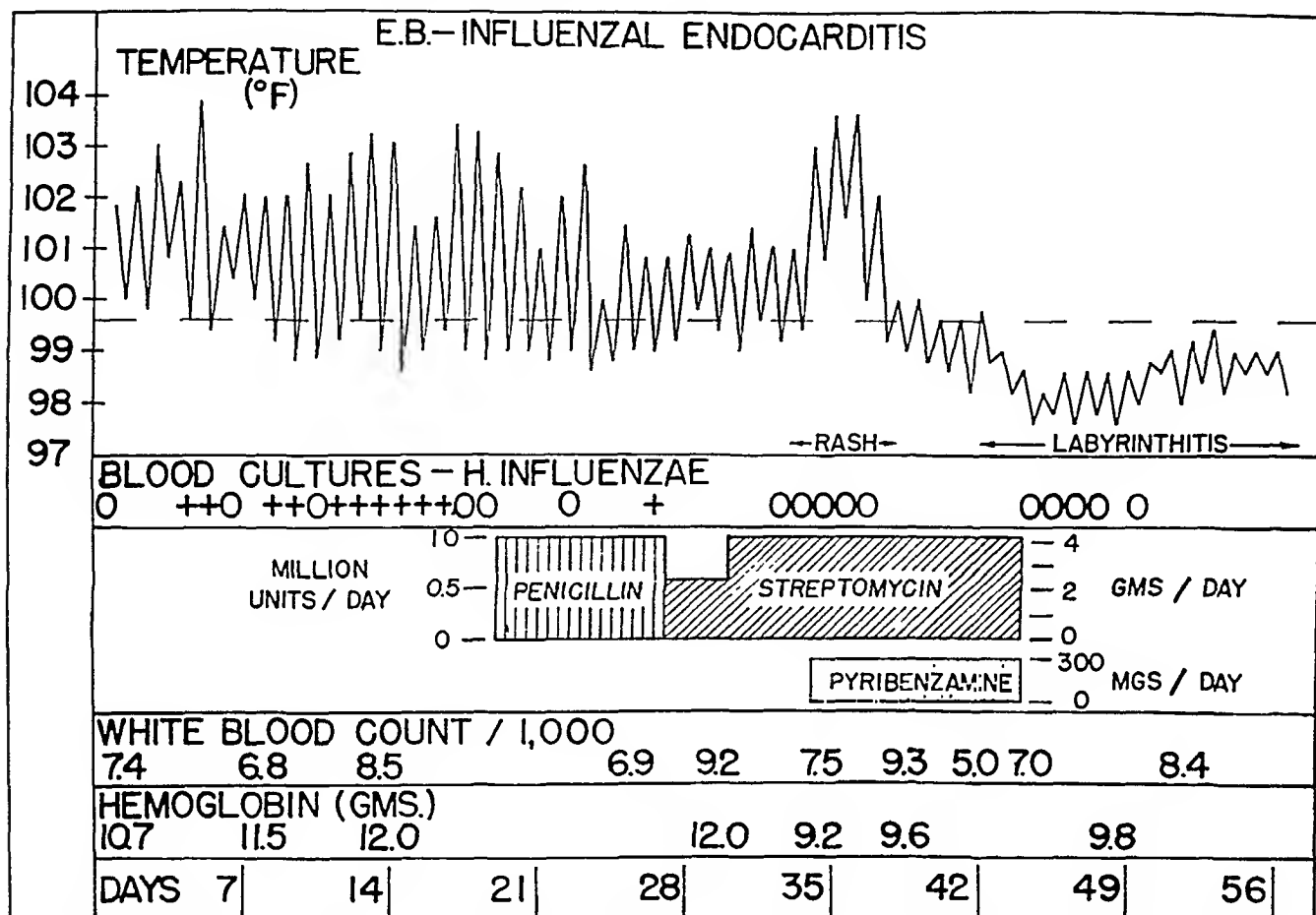


FIG. 1. Chart of the clinical course in Case 1. Note the positive blood culture during penicillin treatment.

latter there was prompt disappearance of the dermatitis and a fall in the temperature to a normal level. On the tenth day of streptomycin administration she first complained of slight dizziness and by the sixteenth day had developed nausea, vomiting and true vertigo. As a consequence streptomycin was stopped on the seventeenth day of treatment, at which time the patient had been afebrile for five days. She remained afebrile for the following two weeks and was discharged from the hospital still suffering from marked vertigo. Although a blood culture during penicillin treatment had been positive, all cultures during and after streptomycin treatment were negative.

At present, more than one year later, she is in good health without evidence of relapse or reinfection. She still has no labyrinthine function but has adapted herself quite well to this loss.

subacute bacterial endocarditis due to a gram-negative organism by means of streptomycin. Several problems presented themselves, first of which was the great difficulty in determining the nature of the infecting organism. The resulting delay, however, gave us an opportunity to observe the inefficacy of penicillin in the dosage administered.

Second, there was the problem of estimating the dosage of streptomycin necessary to effect a cure when the organism was known to be extremely sensitive *in vitro*. The rather large dose finally agreed upon reflected our fear that resistance to the drug might develop rapidly. We could not afford to lose the opportunity to cure this patient by erring on the side of inadequate dosage.

The third problem concerned the complications of streptomycin therapy—fever, dermatitis and labyrinthitis. It is of interest that although the febrile reaction and the skin rash promptly disappeared under treatment with antihistaminic drugs they

entered the hospital on November 10, 1947, because of ten days of fever, chills, weakness and dizziness.

At the age of four he had had an illness diagnosed as rheumatic fever; there were recurrences at eight and twelve. By the age of

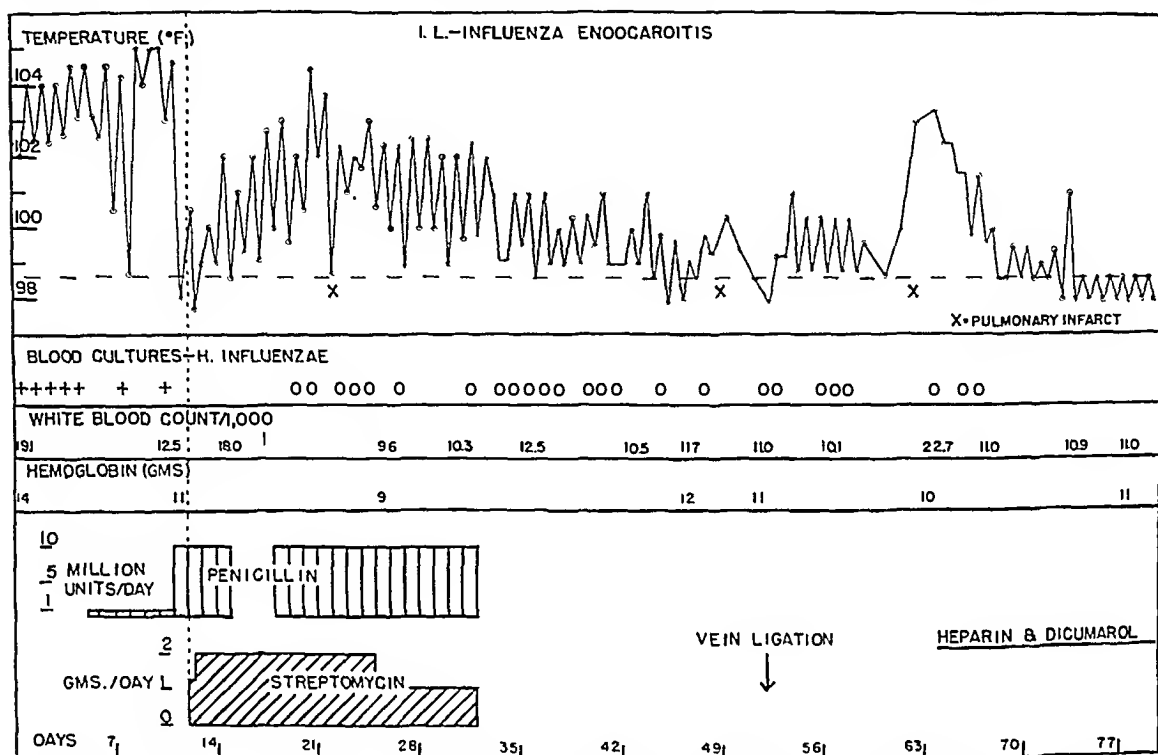


FIG. 2. Chart of the clinical course in Case II. Note the apparent response to the increased dosage of penicillin.

had no effect whatever on the development and progression of labyrinthitis. Streptomycin was continued in the face of increasing vertigo, nausea and vomiting, with full knowledge that the labyrinths were being sacrificed in an effort to cure a uniformly fatal disease. In retrospect, it may well be argued that a similar cure could have been obtained by using a smaller dose of streptomycin, thereby greatly reducing the likelihood of labyrinthitis. It is impossible to answer this question in any individual case but we believe the large dosage was entirely justified here. At any rate the loss of labyrinthine function has not seriously interfered with the patient's normal activities.

CASE II. (Fig. 2.) Mr. I. L. (No. 55578) was a twenty-five year old draughtsman who

seventeen a moderately loud, apical systolic murmur and a faint aortic diastolic murmur had appeared. There were no further episodes of rheumatic fever and he led a sedentary life without symptoms.

In August, 1947 he had an illness characterized by malaise, headache and moderately high fever. There were no localizing complaints. The symptoms subsided in about two weeks and were attributed to "grippe." In November, however, quite suddenly he began to have shivering chills, a fever to 103°F. by mouth, dizziness, weakness and occasional vomiting. He had noticed no skin rash or chest pain; there had been no preceding oral surgery. After ten days of these symptoms he entered the hospital.

On admission he did not appear particularly ill, but his temperature was 103.5°F. by rectum and his pulse was 120, with a regular rhythm. Otherwise his condition did not differ materially from that noted in the clinic in previous

years. There were an aortic diastolic murmur and a questionable mitral diastolic murmur. There was one questionable petechial hemorrhage inside the lower lip; there was no clubbing of the fingers; the spleen was barely palpable.

Laboratory data revealed the following: The white blood count was 20,000 cells per cu. mm., with 80 per cent neutrophils, 7 per cent lymphocytes, 12 per cent monocytes, and 1 per cent eosinophiles. The hemoglobin was 14 Gm. per cent. The urine showed a specific gravity as high as 1.026, no albumin and at most 3 to 5 red blood cells per high power field in the spun sediment. A chest film and electrocardiogram were within normal limits.

The temperature remained between 102 and 104°F. by rectum. On the fifth hospital day, in the absence of a bacteriologic diagnosis but on strong suspicion of bacterial endocarditis, treatment was begun with one million units of penicillin per day by constant intramuscular drip in the anterior thigh. A level of at least 5 units of penicillin per cc. of serum was maintained. After six days of treatment the fever remained high and an alarming lethargy appeared. The hemoglobin had dropped from 14 to 11 Gm. per cent. The dosage of penicillin was increased to ten million units per day, bringing the serum level to at least 10 units per cc. There was a definite clinical response to the increased dosage within twelve hours. The temperature dropped from 104°F. to normal and there was a marked improvement in the patient's alertness and sense of well being.

At the same time, however, it was learned that *H. influenzae* had been identified in all seven of the blood cultures taken since the patient's admission; two of these had been drawn while penicillin was being given at the rate of one million units a day. The organism grew in rough, compact colonies and could not be typed with the existing antisera. *In vitro* it was inhibited by a streptomycin concentration of 1 unit (0.001 mg.) per cc. but grew in a penicillin concentration of 66 units per cc. As soon as the organism was known and before sensitivities were available streptomycin was added at the rate of 2 Gm. a day in divided intramuscular doses of 0.25 Gm. every three hours. The serum level of streptomycin, measured just before administration of one of these doses, was 32 units per cc., or at least thirty-two times the level required to inhibit growth *in vitro*. Penicillin was discontinued for three days, but when the

temperature began to reach daily peaks of 102°F. it was resumed. Although the organism was now known to be one generally considered insensitive to penicillin, the previous response to high penicillin dosage had seemed definite. Streptomycin was given for three weeks, at the rate of 2 Gm. a day for two weeks and 1 Gm. a day for one week; a total of 33.25 Gm. was administered. Penicillin was given by constant drip for a total of twenty-five days, the total dose being 187,000,000 units. The temperature continued to rise to 102°F. daily while chemotherapy was continued; it gradually fell to normal in the two weeks following cessation of treatment. There was no other suggestion of drug sensitivity nor was there evidence of streptomycin toxicity by ordinary clinical standards. He was given several blood transfusions during the course of treatment.

He continued to feel well, in general, but three episodes of pulmonary infarction complicated his recovery. The first occurred while he was receiving chemotherapy and while he was on complete bed rest because of the constant intramuscular drip in the anterior thigh. Pain and tenderness at the injection site were considerable although clinically there was no area of venous thrombosis. Because of the possible danger of subarachnoid hemorrhage, anticoagulant therapy was avoided while the possibility of active endocarditis was present; venous ligation was not performed because of the difficulties likely to follow the intramuscular drip. The second episode occurred three weeks after the cessation of chemotherapy during which time the patient was ambulatory. It was promptly treated by bilateral superficial femoral vein ligation, only to be followed by a third large pulmonary infarct two weeks later. After three weeks of anticoagulant therapy (heparin and dicumarol) he appeared perfectly well, an elevated sedimentation rate being the only abnormal finding. He was finally discharged from the hospital on January 30, 1948.

At present, six months after chemotherapy was stopped, all evidence points to recovery from bacterial endocarditis. All blood cultures have been negative since streptomycin was begun. The sedimentation rate, white blood count and temperature all remain normal. The patient has gained weight and is back at work. A slight aortic diastolic murmur is the only cardiac abnormality discernible. There have been no further episodes of pulmonary infarction.

Comment. It seems probable that streptomycin was the agent responsible for the patient's recovery. His critical condition demanded the continuation of penicillin as well as streptomycin. This was unfortunate for the nicety of the clinical experiment but certain evidence suggests that penicillin did not contribute to his recovery: (1) There were several positive blood cultures after starting therapy with one million units of penicillin per day. (2) The *in vitro* resistance of the organism to penicillin was great (it was not inhibited by 66 units per cc.) and blood levels of penicillin actually obtained did not approach the level which this resistance would seem to require.

On the other hand, there did appear to be a definite clinical response to the institution of heavy penicillin dosage, and it was largely on the basis of this apparent response that penicillin was continued. It is quite possible that the apparent "response" was merely a coincidental variation in the underlying disease. No final conclusions can be drawn since streptomycin was started on the day following the increase in penicillin dosage.

The recurrent pulmonary emboli were a serious complication although not one directly related to the problem of chemotherapy. Their source remained uncertain. The heart itself was a possibility, although an unlikely one, since there was no evidence of a tricuspid or an interventricular septal lesion. There was also no definite evidence to incriminate the veins of the legs but statistically they were the most likely source of emboli. Some question must be raised as to the advisability of using the muscles of the legs to receive a constant intramuscular infusion for long periods during which time bed rest is unavoidable.

COMMENTS

In addition to the present cases nine instances of recovery from bacterial endocarditis due to gram-negative organisms have been reported.³⁻⁷ In three of these the responsible organism was an unclassified gram-negative bacillus; in the other six

either *H. influenzae* or *H. parainfluenzae* was recovered. Streptomycin was used in the treatment of two of the *Hemophilus* patients, although in one of them⁶ the role of streptomycin cannot be determined from the information furnished; in the other,⁷ its role is unequivocal. In the first case presented herein recovery was undoubtedly due to streptomycin; in the second, streptomycin was probably responsible for recovery.

Thus the evidence, although not great in bulk, indicates that streptomycin is highly effective in treating *Hemophilus* endocarditis and is as effective here as in other infections due to these organisms. In fact, three of the four patient's cases now reported (one noted by Hunter,⁶ that of Massell et al.⁷ and the present Case 11) recovered with a relatively moderate dosage of 2 Gm. per day. None of the three showed evidence of permanent eighth nerve injury. We were unable to find any reports of streptomycin failure in *Hemophilus* endocarditis.

It is worth remembering, however, that the sulfonamides and penicillin may at times be of use in *H. influenzae* infections. The possible effectiveness of penicillin was suggested in Case 11. Although penicillin was at first considered to have no effect on *H. influenzae*, there is now a considerable amount of evidence to show that some strains may be strikingly sensitive, both *in vitro* and in meningeal infections.^{8,9} In general, clinical success was associated with high *in vitro* sensitivity.

It has been pointed out by Dienes,¹⁰ however, that most strains of *H. influenzae* which have apparently been inhibited by penicillin will eventually show growth after prolonged incubation even though concentrations as high as 1,000 units per cc. have been used. Hence, penicillin sensitivity as ordinarily determined may be a guide only to the susceptibility of the less resistant organisms in a given strain. It is entirely possible that here and elsewhere penicillin and streptomycin may act synergistically. This sort of "chemotherapeutic crossfire" has already been suggested by Hunter.⁶

SUMMARY

1. Streptomycin is effective in the treatment of bacterial endocarditis due to *Hemophilus influenzae*. It was responsible for recovery in one of the cases presented and probably responsible in the other.

2. Use of other chemotherapeutic agents, particularly penicillin, should not be overlooked in the treatment of *Hemophilus* infections.

Acknowledgments: We would like to express our indebtedness to Dr. Edward F. Bland, for guidance in the preparation of this report, and to Dr. Louis Dienes, in whose laboratory the organisms were identified and the sensitivities and serum levels determined.

REFERENCES

1. DAHL, L. K. Cases from the medical grand rounds, Massachusetts General Hospital. *Am. Pract.*, 1: 498, 1947.
2. PAUL, O., BLAND, E. F. and WHITE, P. D. Bacterial endocarditis. *New England J. Med.*, 237: 349, 1947.
- 3a. BIERMAN, W. and BAEHR, G. Use of physically induced pyrexia and chemotherapy in the treatment of subacute bacterial endocarditis. *J. A. M. A.*, 116: 292, 1941.
- 3b. LICHTMAN, S. S. Treatment of subacute bacterial endocarditis; current results. *Ann. Int. Med.*, 19: 787, 1943.
4. PRIEST, W. S. and MCGEE, C. J. Streptomycin in the treatment of subacute bacterial endocarditis; report of three cases. *J. A. M. A.*, 132: 124, 1946.
5. HUNTER, T. H. and DUANE, R. B., JR. Subacute bacterial endocarditis due to gram-negative organisms. *J. A. M. A.*, 132: 209, 1946.
6. HUNTER, T. H. Use of streptomycin in treatment of bacterial endocarditis. *Am. J. Med.*, 2: 436, 1947.
7. MASSELL, B. F., ZELLER, J. W., DOW, J. W. and HARTING, D. Streptomycin treatment of bacterial endocarditis: report of a case. *New England J. Med.*, 238: 464, 1948.
8. GORDON, M. and ZINNEMANN, K. The in vitro sensitivity of *H. influenzae* to penicillin. With special reference to meningeal strains of Pittman's type b. *Brit. M. J.*, 2: 795, 1945.
9. ZINNEMANN, K. A survey of the outcome of 20 cases of *H. influenzae* meningitis related to bacterial type. *Brit. M. J.*, 2: 931, 1946.
10. DIENES, L. Personal communication.

Multiple Pulmonary Artery Aneurysms*

Endarteritis of Ductus Arteriosus and Congenital Pulmonary Cysts

MARVIN LILLIAN, M.D.

Boston, Massachusetts

THE rarity of pulmonary artery aneurysm was cogently presented in the survey by Deterling and Clagett¹ which disclosed that eight cases of aneurysm were found in 109,571 necropsies gathered from various clinics both abroad and in this country for the period 1846 to 1946. Reports on congenital cysts of the lungs could not be found in American publications by Koontz² until 1925 when he reviewed foreign case reports and collected 108 cases, which aggregation also included allied conditions, such as diverticula of the trachea and bronchi, cysts of aberrant lung tissue, etc.

Necropsy reports on penicillin-treated patients with bacterial endocarditis are still scant. Since an unusual alliance of conditions, viz., widely patent ductus arteriosus with superimposed vegetative endarteritis, saccular aneurysm of the pulmonary artery stem, mycotic aneurysms of the peripheral pulmonary arterial radicles and congenital cyst formation in the lungs has been encountered in the same individual who in the latter part of her illness received intensive antibiotic therapy, the case is considered to be of enough interest to warrant reporting in some detail.

CASE REPORT

A seventeen year old white schoolgirl was admitted to the Peter Bent Brigham Hospital for the first time because of increasing weakness and fever.

The family history was without significance. The past history disclosed that the patient's birth and development were apparently normal except for a cardiac murmur first noted at six months and characterized as having the sound of a "threshing machine." There was no history

of rheumatic fever, scarlet fever or cyanosis. The usual childhood illnesses were experienced without complications.

Approximately seven months prior to admission the patient had an appendectomy performed following an episode of acute abdominal pain. Following the operation the details of which are unknown, the patient continued to feel "run down" but without specific complaints. She thought she had lost some weight during the four to five months prior to entry. About six weeks before admission to this hospital the patient had an upper respiratory infection accompanied by fever. Following treatment with sulfonamides, hematuria is alleged to have occurred; the medication was stopped. Because of persistent fever, the patient was admitted to another hospital. It is reported that "gamma streptococci" were grown from her blood on several occasions. One urine specimen was grossly bloody. During this period she was treated with penicillin in doses of 75 to 100,000 units every three hours; during the week before entry to this hospital she received 150,000 units of streptomycin every four hours. The fever did not subside and the patient had repeated episodes of what were considered to be pulmonary infarctions. The hemoglobin dropped to 40 per cent and rose only slightly with aid of a transfusion. She complained intermittently of pain between the shoulders and pain in the chest on inspiration.

Physical examination revealed the following: temperature, 102°F., pulse, 120; respirations, 24 and blood pressure 115/60. The patient was a poorly nourished, normally developed young white girl who appeared chronically ill and seemed to be in moderate distress. Her cheeks were flushed and there was slight labial cyanosis. There was slight facial asymmetry associated with torticollis. A single petechia was seen in the temporal field of each fundus. The heart was greatly enlarged to the left at both the

* From The Dept. of Pathology, Peter Bent Brigham Hospital, Boston, Mass.

apex and the base. P_2 was loud and snapping and of greater intensity than A_2 . There was a grade iv continuous murmur heard over the pulmonic area and upper precordium and through to the back. A grade iii apical systolic murmur and a snapping mitral first sound were heard. The apical rate was 132 and regular. The inferior border of liver dullness was found to be 3 fingerbreadths below the right costal margin although the inferior liver edge was not palpated. The tip of the spleen was palpated 6 cm. below the left costal margin and was tender. The lungs were clear except for fine basal rales bilaterally. No peripheral edema was present. Moderate arachnodactyly was noted.

Laboratory data was as follows: A serologic test for syphilis (Hinton) was negative; the urine was concentrated to 1.033, there was persistent 1 to 3 plus proteinuria and red and white cells as well as a few granular casts were seen in all sediments. The erythrocyte sedimentation rate was consistently elevated. The hematocrit varied between 29 and 32 rising terminally to 40. The white blood cell count varied from 11 to 15,000 with a normal differential pattern. Routine blood chemistry values were within normal limits. Ten blood cultures and a sternal marrow culture yielded no growth. Nose and throat cultures revealed no significant flora. Blood penicillin levels varied between 5 to 20 units/cc. Electrocardiogram showed left axis deviation. Unipolar chest leads showed unusually high R waves in V_1 and V_2 and elevated S-T segments in V_2 and V_4 . The tracings suggested that the apex of the heart was displaced to the left and posteriorly. The rate was 125, P-R interval 0.16, QRS duration 0.09 seconds. Chest films on admission showed marked enlargement of all borders and the left auricle and ventricle particularly. Fluoroscopy showed a good, regular beat with pulsation of the hilar vessels. There was a marked degree of congestion. Two subsequent films showed increase in basal cloudiness with a trace of fluid at the right base. The venous pressure was 140 mm. of normal saline and the circulation time (magnesium sulfate) was 20 seconds.

The patient's fever persisted despite massive penicillin therapy started on the fifth hospital day. The dosage schedule was 4.8 million units which was increased to 9.6 million units from the eighth through the fourteenth hospital day and maintained at 4.8 million units from the

nineteenth through the twenty-ninth hospital day. She was fully digitalized. A surgical consultant was of the opinion that the patient was not in adequate condition for surgical interference. There was marked tachycardia and tachypnea. On the twelfth and fourteenth hospital days the patient had a series of brisk and copious hemoptyses associated with severe chest pain. She rallied fairly well from these episodes but the fever continued practically unabated. On the twenty-eighth hospital day she had gross hemoptysis again which recurred at frequent intervals, with the production of increasing quantities of blood. The patient expired on the thirtieth hospital day.

Autopsy was performed eleven hours post-mortem; only the salient findings are described.

The cadaver was that of a well developed but poorly nourished young white female who appeared slightly younger than her stated age (seventeen). There was marked pallor of the mucosal and cutaneous surfaces but no petechiae were found. Upon opening the chest, 1,250 cc. of clotted blood were found in the left hemithorax, which had originated from a pleural rent overlying the anterolateral aspect of the left lower lobe; there was no excessive fluid in the right hemithorax.

There was 150 cc. of a slightly turbid, odorless, light green fluid in the pericardial sac which was lined by a smooth lustrous pericardium. The heart weighed 550 Gm. and was uniformly enlarged but not dilated. There were two "soldier spots" in the anterior epicardium of the right ventricle. The valves were all normal except for two glistening, grey, 3 mm. papules on the atrial surface of the posterior mitral leaflet about 2 mm. from the closure edge.

Microscopically, numerous sections of the ventricles, atria and auricular appendages revealed no typical rheumatic stigmas. A few focal areas of myocardial fibrosis were seen usually in relation to the coronary radicles. The "soldier spots" were produced by focal areas of fibrous connective tissue which was slightly hyalinized and with little cellular infiltration. The papular lesion of the posterior mitral leaflet comprised a center of edematous connective tissue in which fibroblasts, capillaries and some neutrophils were seen; the core was surrounded by some fibrin which, in turn, was endothelialized. Examination of the mitral valve lesions stained with a modified Gram's stain failed to disclose any bacteria.

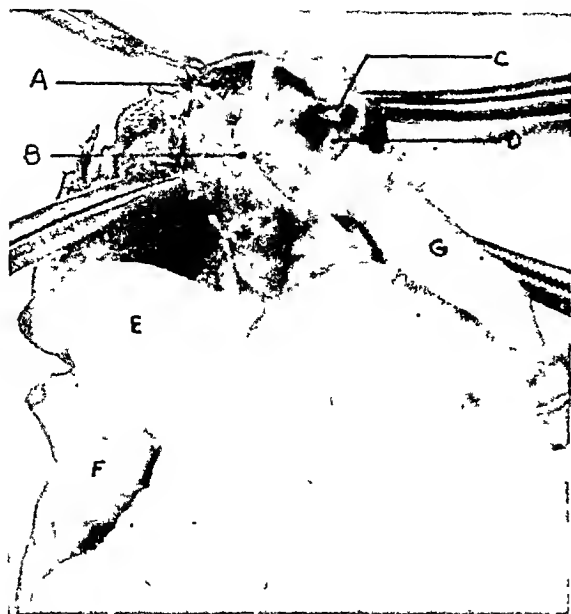


FIG. 1. Anterior aspect of heart with anterior half of pulmonary conus removed. A, clamp mark in fundus of saccular aneurysm; B, proximal margin of aneurysmal mouth showing abrupt loss of media (white); C, ductus arteriosus lumen; D, attachment site of ductal vegetation; E, aorta, F, right auricle; G, intima of pulmonary conus.

Approximately 5 cm. distal to the pulmonary valve ring there was a saccular aneurysm of the pulmonary trunk 0.8 cm. deep with a circular orifice having a diameter of 1.2 cm. (Fig. 1.) The intimal lining of the aneurysm was dull, red-grey and granular. In the area immediately proximal to the aneurysm the intima appeared pitted and reddened but with no evidence of frank ulceration. There was no evidence of media in the aneurysm and the surrounding adventitia was not unduly thickened. Approximately 0.5 cm. distal to the aneurysm the opening of the ductus arteriosus was seen; the latter was short but wide with respective dimensions of 0.3 by 0.6 cm.—virtually a side-by-side anastomosis between the aorta and pulmonary trunk. The ductus inserted into the aorta about 2.0 cm. distal to the origin of the left subclavian artery. An elongated, red-grey and granular vegetation was seen to arise at the pulmonary side of the ductus and extend through it with the free end presenting in the lumen of the aorta; the vegetation measured 0.3 by 0.2 by 0.6 cm. A similar vegetation, but smaller, was seen where the ductus inserted into the aorta. Neither vegetation was remarkably friable.

Microscopically, a section including relatively normal pulmonary artery trunk and the area of transition into aneurysm revealed focal as well

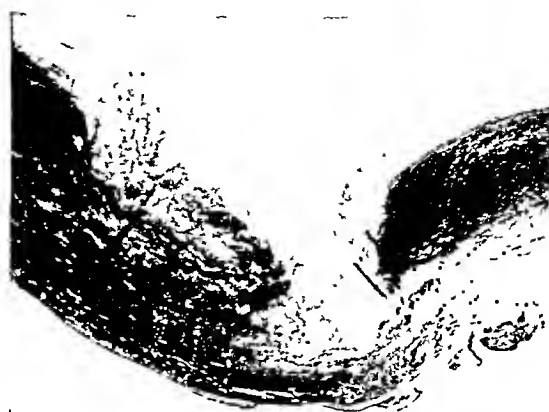


FIG. 2. Photomicrograph of pulmonary artery trunk immediately proximal to the saccular aneurysm showing the prototype of medial destruction. Weigert's elastic tissue stain; $\times 18$.

as diffuse hyalinization of the media. There were focal collections of lymphocytes in the media and adventitia. Macrophages containing hemosiderin were present both in the intima and media. Sections stained for elastic tissue by Weigert's method revealed disruption and irregular distribution of the elastic lamellae in the proximal pulmonary artery with complete absence of elastic fibers in the aneurysm. There was no remarkable alteration of the adventitia or vasa vasorum. Sections of the pulmonary artery proximal to the aneurysm which appeared grossly pitted and reddened disclosed miliary aneurysm formation, the histologic features of which were identical with those described previously. (Fig. 2.) Sections through the origin of the ductus revealed marked intimal proliferation and hyalinization of the pulmonary trunk proximal to the ductus; there was also disruption of the elastic lamellae as well as diminution in quantity. Lymphocytes were seen in the media. As the ductus was reached the appearance of the latter approached that of normal aorta. The ductus vegetation was constituted by a mass of blood cellular debris which was invaded at its base by fibroblasts and capillaries; the vegetation was not endothelialized. No bacteria were seen.

The most striking change was seen in the left lower lobe of the lung which was densely hemorrhagic, with a torn pleural membrane on its anterolateral aspect. (Fig. 3.) Multiple parallel sections were made and these revealed most of the lobe to be occupied by a large multilocular cystic structure lined by a dull grey membranous tissue in which laminated blood clot was present. As the pulmonary hilus was approached it was possible to demonstrate a communication



FIG. 3. Anterior aspect of lung; left lower lobe is cut sagittally revealing cystic appearance of hemorrhagic infarct. Note pleural rent and thickening.

between a radicle of the left lower pulmonary artery and the large hematoma. (Fig. 4.) The actual point of rupture could not be found in the face of the prodigious hemorrhagic infiltration. Communication of the hematoma with a comparably-sized bronchial radicle could not be demonstrated. Similar vascular changes were not seen elsewhere; there was no grossly evident vascular sclerosis. Additional findings in the lungs were: a multilocular cyst in the left upper lobe containing a thin, opalescent fluid which did not communicate with the bronchial tree (Fig. 5); a unilocular cyst in the right lower lobe containing a small blood clot; a recent small infarct of the right middle lobe.

Microscopically, the histologic picture was difficult to interpret because of the intense hemorrhagic infiltration. However, sections stained for elastic tissue by Weigert's method helped to delineate the various architectural features. The lining of the cystic space in the left lower lobe was devoid of epithelium and constituted by a laminated fibrous connective tissue and intimately adherent to the adjacent blood clot which was invaded by fibroblasts and capillaries. Near the fibrous cyst wall there was a small-sized artery which arrested attention by virtue of almost complete loss of internal elastic membrane and media with eccentric dilatation of the vessel wall; the proliferated intima appeared to be apposed to the adventitia in much the same manner as was seen in the large



FIG. 4. Sagittal surfaces of left lower lobe; the probe passes through a left lower pulmonary arterial radicle into the hemorrhagic infarct.

saccular aneurysm. (Fig. 6.) The medium-sized arterial radicle seen in the gross specimen to communicate with the hematomatous cyst could not be positively identified in the microscopic preparations. In addition to this vascular medial change a second deviation from the normal was that of an obliterative intimal proliferation; the latter change was found in all lobes. The multilocular cyst of the left upper lobe was lined by a

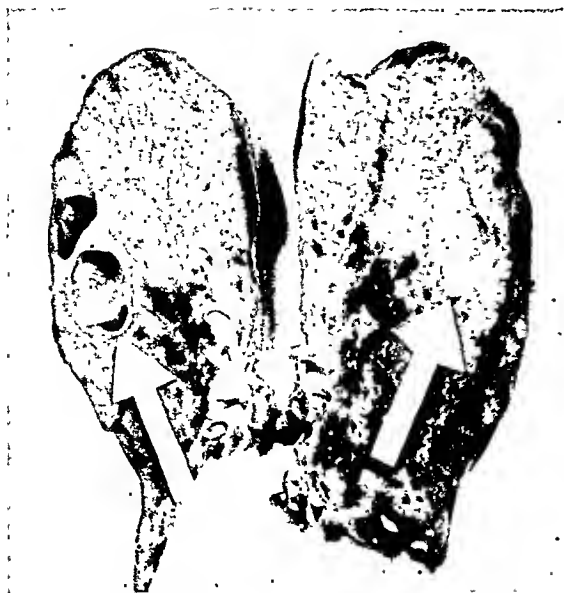


FIG. 5. Multilocular cysts of left upper lobe.

discontinuous epithelium; the epithelial cells were flattened and cuboidal with poor cellular outline and vaguely reminiscent of a syncytium. In close proximity to the cyst wall there were several cuboidal-cell lined spaces somewhat similar to tubo-alveolar ducts. The cyst in the right lower lobe was lined by a discontinuous columnar type epithelium resting on a laminated, fibrous tissue without a definitive membrane propria; the morphology was very similar to bronchial epithelium. Beneath the cyst wall there were several collapsed bronchiallike structures with cartilagenous plaques interposed. In addition the cyst wall was seen to contain hemosiderin-laden macrophages and a few focal collections of lymphocytes. There were many areas of fibrous scarring in other sections of the right lower lobe consistent with the appearance of old, healed pulmonary infarcts.

The kidneys were striking by virtue of their extreme pallor and scattered cortical petechiae; there were no grossly recognizable infarcts.

Microscopically, the dominant lesion was glomerular and consisted of focal to complete hyalinization of the capillary tuft. There was periglomerular lymphocytic infiltration with no evidence of an acute exudative reaction.

The spleen weighed 280 Gm. and was not further remarkable; there were no infarcts grossly or microscopically.

Cultures from the pleural spaces, pericardial cavity, heart blood and lungs yielded no growth. The ductal vegetation was removed with sterile

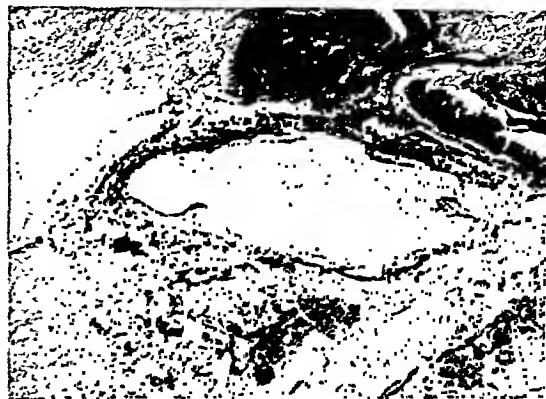


FIG. 6. Photomicrograph of arterial lesion in left lower lobe; note intimal proliferation and loss of media with eccentric dilatation. Weigert's elastic tissue stain; $\times 20$.

precautions, ground in a mortar and incubated in appropriate media for two weeks with no growth observed. The mitral valve papules were smeared and the swabs incubated; no growth was obtained.

Final anatomic diagnoses were: Hemothorax, left; mycotic aneurysms of the peripheral pulmonary arterial radicles; ductus arteriosus with vegetative endarteritis; saccular (mycotic) aneurysm of the pulmonary artery trunk; non-bacterial mitral valvulitis; pulmonary infarcts, recent and old, bilateral; congenital cysts of lungs; focal embolic glomerulonephritis.

COMMENT

Aneurysm Formation in the Pulmonary Vascular Tree. Brenner³ observed that saccular aneurysm formation of the pulmonary artery stem and main branches was exceedingly rare, fusiform dilatation being much more common. He offered the following etiologic classification of pulmonary artery aneurysm formation: 1) Traumatic, rare. 2) Mycotic, aneurysm formation in association with infection of a congenital cardiac defect. 3) Congenital, associated with congenital cardiac defects which are not demonstrably infected but in which weakness of the arterial wall was probably due to congenital deficiency in elastic tissue. 4) Syphilitic, with typical mesarteritis and the demonstration by Warthin⁴ of spirochetes in the media. Excepting Warthin's work, unequivocal demonstration of the pathogenesis of pulmonary artery aneurysm is rarely if ever made. The Boyd and McGavack⁵ survey of

139 cases of pulmonary artery aneurysm indicated syphilis to be a significant factor in only 31.7 per cent of the cases. Deterling and Clagett¹ in a later review of thirty-six cases which they collected showed a comparable incidence of 39 per cent. In the case herein presented there was no historical, clinical or laboratory evidence implicating luetic infection as an etiologic factor.

With regard to the mechanism of mycotic aneurysm formation, Brenner has postulated these pathways: (1) spread by continuity from infective endocarditis of the pulmonary valve; (2) invasion from without by spread from an infective process in the surrounding tissues; (3) invasion through the vasa vasorum; (4) infection reaching the pulmonary vessels from the lumen by means of an infected embolus or the direct implantation of infection in the intima without preceding embolism. The saccular aneurysm described earlier cannot be definitely classed as mycotic or congenital exclusively; both factors may have been involved. The occurrence of a vegetative endarteritis in association with a ductus arteriosus suggests that the aneurysm resulted from the interplay of such factors as infection of the arterial wall and pressure of blood reflux through the ductus although congenital deficiency of elastic fibers cannot be ruled out. The morphology of the aneurysm with the abrupt change in disposition of the elastic lamellae not associated with the bifurcation of a vessel is more strongly in favor of the acquired nature of the lesion. The proximity of the saccular aneurysm and the site of the ductal vegetation indicates that infection by direct contiguity was the likely avenue of infection.

The histologic identification of the peripheral pulmonary arterial radicle which communicated with the hematomatous cyst of the left lower lobe was not possible because of the situation of the lesion in a markedly hemorrhagic tissue. Yet demonstration of the medial disease in smaller-sized vessels in the immediate area of the larger artery which was histologically comparable to the saccular aneurysm of the pulmonary artery

stem inevitably directs to the conclusion that similar changes occurred in the larger radicle.

Another factor which has been considered in the genesis of aneurysm formation in the pulmonary tree is that of atherosclerosis. Deterling and Clagett described the presence of atherosclerosis in the right pulmonary artery (site of aneurysm) and microscopically in the arterioles of both lungs in their case. In view of Brenner's finding of arteriosclerosis microscopically in the pulmonary vessels in 97 per cent of one hundred consecutive unselected autopsy cases (a group which included some children) the exact position of atherosclerosis in a cause-effect relationship with pulmonary artery aneurysm formation is somewhat obscure.

The absence of any anatomic evidence of pulmonary tuberculosis serves to exclude the possibility of a Rasmussen aneurysm—aneurysm in the wall of a tuberculous cavity and an important cause of the brisk hemoptysis seen in clinical pulmonary tuberculosis.

Cyst Formation in the Lungs. The multiple pulmonary cysts encountered in the case reported which were found to be lined by a variegated epithelium or none at all in the absence of demonstrable bronchial disease or other parenchymal affection (excepting infarct) hints very strongly to their congenital nature. To be sure the determination of the nature of a pulmonary cyst in the adult is almost never definitive, as Koontz pointed out. The difficulties are such that the validity of the concept of congenital cystic formation in the lungs has been questioned by some; certainly there is far from unanimity of opinion regarding the etiologic factors in certain pulmonary cystic structures. Be that as it may, the process appears to occur more frequently than was considered at the time Koontz published his report on congenital cysts of the lungs. Thus, in the decade following Koontz' paper, King and Harris⁶ collected 152 cases of cystic formation in the lungs. Additional papers on this subject have been published by

Schenck,⁷ Smith,⁸ Stanford and Nalle⁹ and Ruschin.¹⁰

Cysts of the lungs of established etiology, e.g., hydatid, dermoid, bronchiectatic, etc., should not be confused with the congenital variety. Koontz cited the following terms used synonymously: fetal bronchiectasis, congenital cystic formation of the lungs, atelectatic bronchiectasis, congenital bronchiectasis, honeycomb lungs, etc.; he concluded from the foregoing that the varied nomenclature depended on the pathogenetic interpretations of the various investigators. King and Harris believed that the condition resulted from an anomaly which interrupts the canalization of a ramification of the embryonic bronchial radicle leading to obstruction of the distal portion of the pulmonary buds which develop more completely. There being no bronchial outlet the accumulated secretions then distend the space they are formed in which results in encroachment and compression of the surrounding pulmonary tissue. Norris and Tyson¹¹ studied polycystic disease in two infants by means of numerous serial sections and compared them with polycystic disease of the kidney, liver and pancreas; they concluded that “. . . polycystic disease is a pathologic manifestation of normal fetal resorption and degeneration.”

The cyst wall is constituted of an epithelial layer made up of columnar cells with or without cilia, cuboidal cells, flattened cells or no epithelium at all with bare connective tissue forming the lining. Koontz believed that the lack of pigment in the congenital lesions indicates that the affected part had never functioned and that therefore the pathologic condition antedated birth. Ruschin pointed out that the occurrence of pulmonary cysts in the stillborn and newborn as proved by autopsy is probably the strongest evidence in favor of the congenital nature of this disorder.

Thus, in the absence of any demonstrable cause for the acquired nature of the pulmonary cysts in this case, their congenital origin is implied.

Effects of Penicillin on the Course of Bacterial

Endocarditis. The finding of a sterile vegetation which appeared to be well organized and the absence of an exudative reaction in the vascular lesions (including the glomeruli) is in accord with the observations of recent investigators, Geiger and Durlacher¹² and Moore.¹³ This writer agrees with Geiger and Durlacher who believe that the infectious component of bacterial endocarditis is eradicable with penicillin.

The reconstruction of events as they occurred in the case reported herein appears to be as follows: Vegetative endarteritis developed at the mouth of the ductus arteriosus in the wake of the episode of acute appendicitis which was treated by appendectomy. This lesion served as the nidus for the subsequent dissemination of infectious emboli and bacteria which ultimately caused the vascular disease manifested by aneurysm formation, pulmonary infarctions and focal embolic glomerulonephritis. That the infectious process was eventually controlled—but too late—by intensive antibiotic therapy is suggested by the absence of acute inflammatory and minimal presence of chronic inflammatory reaction in the vascular lesions, the lack of exudative reaction in the kidneys, the sterility of the ductal vegetation and the absence of bacteria in histologic preparations of the latter. Ordinarily pulmonary infarcts do not rupture through the visceral pleural membrane; however, such a development did occur in this patient and caused fatal hemothorax. The occurrence of pulmonary cysts in the right lower and left upper lobes suggests that similar cysts in the left lower lobe confronted with the mass of an expanding hematoma caused by a mycotic aneurysm could not maintain their integrity and ruptured, the sanguineous homologue of spontaneous pneumothorax resulting from the rupture of a subpleural bulla.

SUMMARY

A case is described in which multiple mycotic pulmonary artery aneurysms were found in association with vegetative endarteritis of a widely patent ductus arteriosus;

there were concomitant congenital pulmonary cysts. Death resulted from rupture of a peripheral pulmonary arterial branch producing a large hemothorax.

In view of the massive penicillin therapy administered to the patient the histopathologic appearance of the vascular and visceral lesions suggests that the infectious element of bacterial endocarditis was eradicable by use of appropriate antibiotics.

An interpretation of the clinicopathologic sequence of events is offered.

Acknowledgment: The writer wishes to acknowledge the criticism and counsel given by Dr. Alan R. Moritz, Pathologist-in-Chief to the Peter Bent Brigham Hospital, in the preparation of this report.

REFERENCES

1. DETERLING, R. A., JR. and CLAGETT, O. T. Aneurysm of the pulmonary artery: a review of the literature and report of a case. *Am. Heart J.*, 34: 471, 1947.
2. KOONTZ, AMOS R. Congenital cysts of the lung. *Bull. Johns Hopkins Hosp.*, 37: 340, 1925.
3. BRENNER, O. Pathology of the vessels of the pulmonary circulation. II, v. *Arch. Int. Med.* 56: 457, 1189, 1935.
4. WARTHIN, A. S. Syphilis of the pulmonary artery: syphilitic aneurysm of the left upper division: demonstration of *Spirocheta pallida* in wall of the artery and aneurysmal sac. *Am. J. Syph.*, 1: 693, 1917.
5. BOYD, L. J. and MCGAVACK, T. H. Aneurysm of the pulmonary artery; a review of the literature and report of two cases. *Am. Heart J.*, 18: 562, 1939.
6. KING, J. C. and HARRIS, L. C., JR. Congenital lung cyst. *J. A. M. A.*, 108: 274, 1937.
7. SCHENCK, S. G. Diagnosis of congenital cystic disease of the lung. *Arch. Int. Med.*, 60: 1, 1937.
8. SMITH, W. A. Cystic disease of the lung. *Internat. Clin.*, 1: 144, 1942.
9. STANFORD, W. R. and NALLE, B. C., JR. Some notes on cystic disease of lung. *Ann. Int. Med.*, 17: 65, 1942.
10. RUSCHIN, L. J. The cystic lung. *California & West. Med.*, 59: 62, 1943.
11. NORRIS, R. F. and TYSON, R. M. The pathogenesis of congenital polycystic lung and its correlation with polycystic disease or other epithelial organs. *Am. J. Path.*, 23: 1075, 1947.
12. GEIGER, A. J. and DURLACHER, S. H. Fate of endocardial vegetation following penicillin treatment of bacterial endocarditis. *Am. J. Path.*, 23: 1023, 1947.
13. MOORE, ROBERT A. Cellular mechanism of recovery after treatment with penicillin. *J. Lab. & Clin. Med.*, 31: 1279, 1946.

Relapsing Febrile Non-suppurative Panniculitis*

(Weber-Christian Disease)

SAMUEL H. RUBIN, M.D.† and JOHN H. BLAND, M.D.‡

Asbury Park, New Jersey

Burlington, Vermont

DESPITE the fact that Weber-Christian disease is considered rare, we have seen two cases within a period of two months. In this paper we will discuss the pathologic and clinical findings in these patients. Treatment will be described and an attempt will be made to evaluate an apparent etiology.

Since the first report of this pathologic entity was made in 1892 by Pfeifer,¹ approximately thirty-one cases have been cited. A complete review of the cases to 1943 was made by Miller and Kritzer.² This article is significant, too, in that it reports the first autopsy of a patient with acute lesions of Weber-Christian disease. The autopsy findings revealed focal necrosis and fatty changes in the liver, hydropic degeneration of adrenal cortex cells and large numbers of red cells in the fixed members of the reticuloendothelial system. Possible etiologies of the disease were considered as follows: (1) iodides and bromides; (2) foci of infection; (3) avitaminosis. However, the authors believe that because sulfonamide compounds failed to affect the disease, its infectious origin is doubtful.

The second autopsy findings reported by Spain and Foley³ showed fatty changes in the viscera. Necrotic areas in the mesenteric, omental and pretracheal fat were noted, as well as necrotic areas in the subcutaneous fat. In this case the patient developed nodules after having been hospitalized for

uremia of which he subsequently died. Examination of the kidneys disclosed end stages of chronic glomerulonephritis.

Various methods of treatment have been suggested for this disease. Arnold⁴ used sulfadiazine and sulfathiazole without results in a patient who showed severe vascular damage in the nodules. However, he found that the patient responded to sulfapyridine. On five occasions sulfapyridine was withheld and relapses followed. During each relapse this patient had an elevation of the sedimentation rate. Each time the drug was resumed remission ensued within twenty-four hours.

Zee's⁵ patient with leukopenia was treated with sulfadiazine without apparent affect. He tried penicillin and his report is the first one of panniculitis treated with this drug. A total of 2,360,000 units was given. After three and one-half months following cessation of the treatment there was no recurrence of lesions or symptoms.

The case of the most marked leukopenia was described by Friedman.⁶ He found no elevation in the sedimentation rate. His patient had panniculitis for five years previous to her death; she died of staphylococcal septicopyemia after removing a crusted "keratosis" with a razor.

One patient with Weber-Christian disease whose case was reviewed by Larkin et al.⁷ recovered spontaneously after six months. However, the case in the literature which

*From The Station Hospital, Camp Hood, Texas.

†Now at New York Medical College, New York, N. Y.

‡Now at University of Vermont Medical School, Burlington, Vt.

showed the most generalized involvement proved fatal to the patient. This case was reported by Mostofi and Engleman.⁸ Although the patient in this instance had a normal sedimentation rate and negative blood cultures, recurrent fever was present over a period of seven months, during the last two months of which the cutaneous lesions had appeared. The patient received sulfadiazine and penicillin without effect.

Following are the reports of two cases; one of the patients was treated with penicillin and streptomycin. As far as we know this is the first patient with panniculitis treated with streptomycin.

CASE REPORTS

CASE I. The patient was a thirty-two year old, white housewife who came to the female medicine clinic complaining of outbreaks of subcutaneous nodules over a two and one-half-year period. Her family history revealed that her mother died of a pulmonary embolism three months after childbirth. The patient's father has rheumatism, heart trouble and had profuse bleeding at the time of extraction of his teeth. One sister was a blue baby who died soon after birth; one aunt died of pulmonary tuberculosis. One sister and two brothers are living and well. The previous personal history showed that the patient had the usual childhood diseases and frequent epistaxis, the last episode occurring at the age of twenty-one. Onset of the menarche was at eleven years of age and the periods have been normal. A history of chronic constipation was noted for which the patient took various laxatives and mineral oil. In 1944, for a period of one year, she took approximately two tablets of alkaseltzer every two or three days because of a "sour stomach" after eating.

Previous nodules and blisters were described by the patient. Since 1935 she noticed that she bruised easily and occasionally a nodule formed in an ecchymotic area. In 1943, while working in a plant dehydrating carrots and occasionally cabbage, she had an attack of "itching water blisters" on her legs, abdomen, hips and arms. A physician at that time diagnosed the complaint as "carrot poison."

This patient's present illness began two and one-half years ago with outbreaks of subcu-

taneous nodules which were painful. The overlying skin was red. Since the onset, the patient has never been free of some nodules, each persisting about four to five days. However, a few larger ones persisted for about two to three weeks before disappearing and these left a tan tint to the skin for a few months. No pattern of distribution was found by the patient as nodules appeared practically all over her body.

No chills accompanied the nodules although at times the patient felt warm. Nevertheless, she did not take her temperature until instructed to do so at the clinic. She then discovered that she had a low grade fever on several occasions. This was two and one-half weeks before her hospital admission.

Physical examination was essentially negative except for mild obesity and a few scattered subcutaneous nodules over the lower extremities. These nodules were firm, moderately tender, and about 2 to 3 cm. in diameter. The nodules were not attached to the overlying skin which was slightly red. No pattern of distribution was seen.

Initial laboratory studies revealed an erythrocyte count of 3,500,000; hemoglobin was 13 Gm. and there was a leukocyte count of 7,400, with 72 neutrophils and 28 lymphocytes. Sedimentation rate was 3 mm. in one hour (Wintrobe). Blood Kahn was negative; blood culture showed no growth after one week and the urine was normal.

A biopsy of a nodule of the left leg was taken and sent to the Fifthcenth Histopathologic Center, Brooke General Hospital. The specimen was diagnosed as an acute non-suppurative panniculitis. The description of the microscopic section was as follows: "The specimen consists of fatty tissue, which is infiltrated with large numbers of neutrophils and a few eosinophiles. There is likewise considerable hemorrhage and the blood vessels in the fat are engorged. In one region there is a large collection of neutrophils and red blood cells resembling a micro-abscess." The biopsy wound failed to heal for about two and one-half weeks. No apparent infection was visible. (Fig. 1.)

Then a second biopsy was made of a nodule of the left leg and the specimen sent to Brooke General Hospital. The diagnosis again was acute non-suppurative panniculitis. "The pathological picture in this case is essentially similar to that described in the previous biopsy. The clinical history and pathological findings in this case

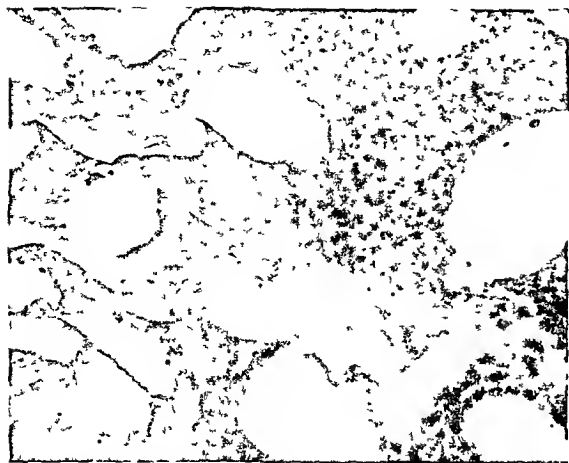


FIG. 1. Photomicrograph of section from nodule of left leg of Case 1 showing fatty tissue with large number of neutrophils.

are thought to be consistent with a diagnosis of Weber-Christian disease. In this case, however, the acute inflammatory elements are much greater than in those reported in the literature." This second biopsy wound took about three weeks to heal, during which time there was a thin, yellow, apparently non-purulent drainage.

On August 27, 1947, the patient was admitted to Camp Hood Station Hospital for treatment with penicillin, as suggested in a previous favorable report.⁵ On August 28th, 30,000 units of penicillin were started intramuscularly every three hours. The temperature became normal soon after the start of the drug. The nodules became fewer in number and lasted about one day whereas they had previously lasted four to five days. Dental and ear, nose and throat examinations at this time failed to reveal any focus of infection. An electrocardiogram was within normal limits. A barium enema was negative of results. The basal metabolic rate was plus 1 and the blood cholesterol was 287 mg. per cent. On September 17th penicillin was discontinued after the patient had received 4,600,000 units over a period of eighteen days. Attention is called to the fact that this is twice the amount given by Zee. It was believed that in our patients there was marked improvement but not a complete cure.

Because the patient was not entirely cured, on September 17th, 0.5 Gm. of streptomycin was given intramuscularly every three hours. On September 19th the temperature went up to 100.4°F. (oral) and on September 20th to 101.6°F. (oral). The same day an indurated area was noticed on the right upper arm at the

site of a previous streptomycin injection. After this the patient began having aching pains in her elbows, hips and knees although no swelling of the joints was visible. On September 21st streptomycin was discontinued due to toxic reactions and the patient received benadryl instead. The patient continued to have a temperature up to 101°F. (oral) daily until the 24th, and then the temperature dropped to normal. Between the end of streptomycin injections and the return to normal of the patient's temperature (a period of three days) the patient developed nodules on the buttocks where she had received the streptomycin. These nodules appeared larger and more tender than any previous ones. Examination of two blood cultures was negative. The patient's white blood count went up to 17,600 and 19,000, respectively, with a shift to the left during elevation of temperature.

On September 30th, six days after the temperature was normal, 0.25 Gm. of streptomycin was started again and was given intramuscularly every three hours. On October 2nd the patient began having aching pains in both knees. On October 3rd she developed an area of anesthesia over the anterior surface of the left thigh, 5 cm. by 3 cm. The drug was discontinued again because of toxic reactions, after the patient had received 23 Gm. *in toto*. On October 4th she developed mild tinnitus.

The patient continued to get an occasional small subcutaneous nodule on one of the extremities. Her temperature went up to 99.8°F. (oral) on the 6th and to 100.2°F. (oral) on October 7th; there were chills. The temperature then returned to normal. This time the patient developed many large tender indurated masses on her thighs where she had received streptomycin. On October 13th one of the masses felt cystic and it was aspirated. Purulent material, over which a layer of fatty material floated, was found. Following aspiration the patient decided to return to her home in the northwest and she will be followed subsequently in the medical clinic.

CASE II. The patient was a twenty-eight year old white woman who considered herself to be in good health until 1939 when she first noted the occurrence of red areas on the anterior aspects of both legs. These lesions were acutely tender, they varied in size from 3 to 4 mm. to 5 or 6 cm. in diameter and were noted to disappear in two to three weeks with concomitant occurrence of new lesions. There have been as

many as fifty or sixty lesions at the same time and as few as three or four. The nodules were subcutaneous and not fixed to the skin. There was no scarring or depression of the skin manifested clinically when the lesions disappeared. The first episode lasted approximately four months and the patient spontaneously became asymptomatic. Since that time, the patient has had five such episodes lasting three to four months, each of which has occurred about every two to three years. The patient believes that she has had fever with each appearance of the nodules and frequently in the intervals between these episodes.

Since 1943, the patient has had recurrent episodes of joint pain which are limited to the hip, knee and ankle joints. The pain is sudden in onset and is not accompanied by swelling or redness although there is tenderness in the involved joints. The pain is migratory and ceases as promptly as it appears. It has lasted from a few hours to twenty-five or thirty days. This symptom has occurred both independently and in association with the subcutaneous nodules. A diagnosis of rheumatic fever was made in another hospital in July, 1946. At this time the patient had a severe attack characterized by fifty to sixty acutely tender, inflamed, subcutaneous nodules limited to the lower extremities. A biopsy was not made at this time.

The past medical history disclosed that the patient has had severe, recurrent sore throats all her life, characterized by fever, dysphagia, generalized aching, malaise and slow convalescence. She complained of dyspnea on mild exertion since 1942. There was rather marked fatigue and slowly progressive asthenia. No familial or environmental factors were elicited. The patient has had two normal, uneventful pregnancies.

The patient was a well developed, well nourished white female. The thyroid gland was moderately and diffusely enlarged. The ocular fundi were normal. Her lung fields were clinically normal. Examination of the heart disclosed a short, high-pitched systolic murmur in the fourth interspace to the left of the sternum. The second pulmonary sound was of greater intensity than the aortic. There were several red, tender areas about both knees. These were subcutaneous nodules not fixed to the skin, and they varied in size from 3 mm. to 3 cm. in diameter. The peripheral pulses were normal. The temperature was 99.4°F. (oral).

Blood count revealed 4,300,000 erythrocytes; 13.0 Gm. hemoglobin; 7,650 leukocytes with 56 per cent polymorphonuclear cells and 44 per cent lymphocytes. Repeated counts were essentially the same and the blood Kahn was negative. All urinalyses were normal. Blood chemistry studies, including a blood urea nitrogen, fasting blood sugar, serum cholesterol and total serum proteins, were normal. The sedimentation rate varied from 9 mm. to 18 mm. (Wintrobe). Examination of two blood cultures was negative. Basal metabolic rate was plus 5. X-ray films of the chest, knees and ankles were interpreted as normal.

Serial electrocardiograms recorded during severe tonsillitis and pharyngitis have demonstrated a P-R interval of .22 seconds, flat T₂ and inverted T₃ and T₄, with a deviation of the electrical axis to the left and low voltage QRS complexes. The tracings have been interpreted as representing the lowest grade of atrioventricular block and evidence of an existing myocarditis secondary to the tonsillitis. One month later the P-R interval was .18 seconds but low QRS complexes persisted. The patient received a total of 1,620,000 units of penicillin intramuscularly, using 30,000 units at three-hourly intervals as treatment for the tonsillitis. Streptococci were not found in repeated throat cultures.

Biopsies were obtained of one small nodule of one week's duration and of another that had been present for two months. Microscopically, the first specimen "consists of a fibrous and adipose tissue, in one region of which are a considerable number of macrophages with a pale-staining, foamy cytoplasm. In addition, there are considerable numbers of lymphocytes and a few eosinophiles and plasma cells. These appear to be in greatest concentration along the fibrous septae of the fat. In one of the fibrous septa a small blood vessel is cut in longitudinal section, and a considerable number of inflammatory cells are around this, also." The second specimen "consists of a fibrous and adipose tissue, in which there is a much greater degree of fat necrosis and inflammatory cell involvement than in the previous section. Many giant cells are seen, with peripherally-placed nuclei. Many macrophages with a pale, foamy cytoplasm are seen, and in addition, there are large numbers of lymphocytes and lesser numbers of eosinophiles and plasma cells." (Fig. 2.)

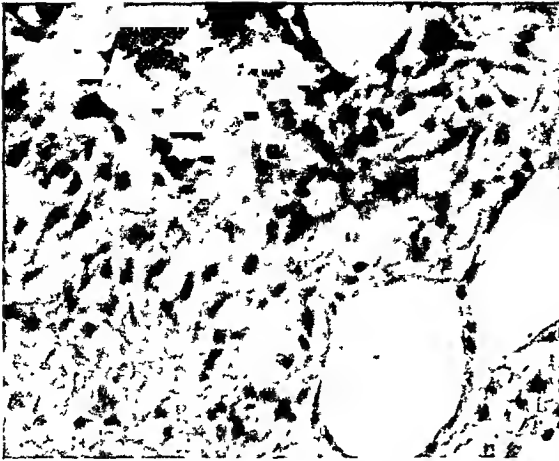


FIG. 2. Photomicrograph of section from nodule of leg of Case II showing a considerable number of macrophages, lymphocytes and a few eosinophils and plasma cells.

The present episode is of three months' duration and the patient has continued to have three to five nodules continuously, with new lesions appearing as the older ones disappear. The patient has refused any further therapy but is seen periodically in the medical clinic.

COMMENTS AND CONCLUSIONS

The cases herein described conform, we believe, to the clinical and histologic criteria ascribed to Weber-Christian disease. From our study of this disease in our patients and in the literature we believe we are justified in drawing the following conclusions:

The first conclusion concerns the etiology of this disease. In the literature causes have been postulated as follows: (1) iodides and bromides; (2) foci of infection; (3) avitaminosis; (4) disturbance of fat metabolism; (5) undetermined specific infectious process and (6) bacterial allergy. Our cases seem to fall into the category of infectious process of

undetermined origin. Support of this etiology is shown by the apparent response of Case I to penicillin. This drug effected a return to normal temperature and a decrease in the number and size of the nodules. The fact that Case II failed to show a response can probably be attributed to the small dosage of the drug given and to the patient's refusal of further treatment.

Second, we believe that the dosage of streptomycin was probably sufficient to prove that it was non-effective. As was described, this drug caused no changes in the nodules.

Third, we conclude that this disease may become generalized, occurring wherever fatty tissue is present. Support of this conclusion is found in the autopsy reports of Spain and Foley³ and Mostofi and Engleman.⁸

REFERENCES

1. PFEIFER, V. Ueber ein Fall von herdweiser Atrophie des subcutanen Fettgewebes. *Deutsches Arch. f. klin. Med.*, 50: 438-449, 1892.
2. MILLER, J. L. and KRITZLER, R. A. Nodular non-suppurative panniculitis. *Arch. Dermat. & Syph.*, 47: 82-96, 1943.
3. SPAIN, D. M. and FOLEY, J. M. Nonsuppurative nodular panniculitis (Weber-Christian's disease). *Am. J. Path.*, 20: 783-787, 1944.
4. ARNOLD, H. L., JR. Nodular nonsuppurative panniculitis (Weber-Christian disease). *Arch. Dermat. & Syph.*, 51: 94-99, 1945.
5. ZEE, MAURICE L. Nodular nonsuppurative panniculitis treated with penicillin. *J. A. M. A.*, 130: 1219-1220, 1946.
6. FRIEDMAN, N. B. Fatal panniculitis. *Arch. Path.*, 39: 42-46, 1945.
7. LARKIN, V. DE P., DE SANCTIS, A. G. and MARGULIS, A. E. Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease). *Am. J. Dis. Child.*, 67: 120-125, 1944.
8. MOSTOFI, F. K. and ENGLEMAN, E. Fatal relapsing febrile nonsuppurative panniculitis. *Arch. Path.*, 43: 417-426, 1947.

Editorial

Disinfection of the Air with Triethylene Glycol Vapor

THE present premature large-scale commercialization of glycol vapors for prevention of acute respiratory disease, together with the accompanying propagation of much misinformation concerning the use and effects of this form of aerial disinfection, make it seem particularly appropriate to review our knowledge of the field. Furthermore, in the two and one-half years intervening since a previous summary of this subject,¹ considerable new information has been acquired.

Among the many chemical compounds which have been tested as vapors or mists for their lethal action on air-borne infectious particles triethylene glycol still remains the agent of choice for use in environments occupied by human beings. Germicidal concentrations of this vapor are odorless, tasteless, non-irritating, non-toxic, invisible and have no deleterious effect on walls, fabrics, books or other objects in the treated space. The presence of as little as 1 cc. of vaporized triethylene glycol in several hundred million cc. of air is, under laboratory conditions, highly lethal for the common respiratory bacteria, pathogenic and non-pathogenic, as well as for the viruses of influenza,¹ psittacosis and meningopneumonitis.² Other bacteria including *Bacillus*

coli and *subtilis* (vegetative form), a number of common non-pathogens of the air and certain molds appear to be susceptible to the action of the vapor.³ No reports have been made of such studies on air-borne tubercle bacilli. Naturally occurring dust-borne bacteria have been found to be much more resistant to the killing action of the vapor than are those experimentally dispersed into the air.

The recent development of certain quantitative technics for study of this subject has made possible much more precise experimentation, the results of which amplify previous knowledge of the activity of triethylene glycol vapor and provide new interpretations. First, fundamental to a more exact understanding of its germicidal effects was determination of the amounts of glycol vapor which could exist in the air at varying humidities and temperatures. By means of a suitable method devised for this particular purpose⁴ curves were constructed indicating the saturation concentrations of triethylene glycol under conditions of relative humidity from 0 to 90 per cent and at temperatures from 20°C. to 29°C. It was found that increasing humidity resulted in

¹ ROBERTSON, O. H. New methods for the control of air-borne infection with especial reference to the use of triethylene glycol vapor. *Wisconsin M. J.*, 46: 311-317, 1947.

² ROSEBURY, T., MEIKLEJOHN, G., KINGSLAND, L. C. and BOLDT, M. H. Disinfection of clouds of meningopneumonitis and psittacosis viruses with triethylene glycol vapor. *J. Exper. Med.*, 85: 65-76, 1947.

³ BIGG, E. and MELLODY, M. Fungicidal action of triethylene glycol. *J. Infect. Dis.*, 79: 45-56, 1946.

⁴ PUCK, T. T. and WISE, H. Studies on vapor liquid equilibria. I. A new dynamic method for the determination of vapor pressure of liquids. *J. Phys. Chem.*, 50: 329-339, 1946.

a progressive although not straightline diminution in quantity of glycol vapor required to saturate the air. Raising the temperature was found to increase the capacity of the air to hold glycol.⁵ With these data available chemical analyses of glycol-containing air could then be interpreted in relation to per cent saturation—a figure which has been found to be much more significant in respect to bactericidal effect than was the absolute quantity of glycol in the atmosphere.

Another important advance was the further development of the glycostat, or glycometer, an instrument for measuring and controlling the concentration of triethylene glycol vapor in the air.⁶ This instrument is extremely sensitive, being capable of detecting as little as 1 microgram of glycol/L. of air under ordinary conditions of humidity and temperature and responds rapidly to changes in concentration of vapor. By means of attachment to a recording device the glycometer provides a continuous record of the concentration of glycol in the atmosphere in terms of per cent saturation. It can be used also to control the output of the glycol vaporizer. Unfortunately this apparatus is not yet commercially available.

Employing the glycostat in specially constructed experimental rooms in which atmospheres could be maintained at any desired temperature and relative humidity, a large series of observations has been made on the bactericidal and virucidal action of varying concentrations of glycol vapor under a wide range of environmental conditions. Optimum conditions for the rapid action of the glycol vapor at ordinary room temperatures were found to be relative humidities of 15 to 40 per cent and vapor saturations of 40 to 100 per cent. In such atmospheres freshly atomized bacteria were

killed in two to three minutes; 80 per cent or more of them were destroyed in the first minute. At high relative humidities (60 to 80 per cent) the rate of action was much reduced but still appreciable. Likewise, at very low humidities (5 to 10 per cent) killing was somewhat retarded. The more nearly the concentration of the glycol vapor in the air approached the saturation value the more rapid the kill. However, the increase in effectiveness at levels about 70 per cent was slight.⁷

Observations of an analogous nature on influenza virus in which white mice were exposed to atmospheres containing freshly atomized virus and glycol vapors showed that the presence of the glycol in the air at saturations of 70 to 90 per cent afforded the mice complete protection against lethal concentrations of the virus. Protection was optimum at relative humidities of 15 to 40 or 50 per cent, as was the case with bactericidal activity of the glycol. However, at high humidities, 70 to 80 per cent, the glycol had relatively little effect as most of the test mice died even when the air was saturated or supersaturated with triethylene glycol. Under optimum conditions of humidity and glycol saturation the virucidal action of the vapor was found to be very rapid.⁸

Studies with dried bacteria in the form of droplet nuclei or as a fine dust made from desiccated saliva suspensions have shown them to be about as susceptible to the lethal action of triethylene glycol vapor as are freshly atomized suspensions. The importance of this finding lies in the fact that most pathogenic bacteria present in an infected atmosphere are probably in the dried state.⁸

These more recent observations bring out the fact that, in adequate concentrations, triethylene glycol vapor is effective over a wider range of relative humidities

⁵ WISE, H. and PUCK, T. T. The saturation concentrations of triethylene glycol vapor at various relative humidities and temperatures. *Science*, 105: 556-557, 1947.

⁶ PUCK, T. T. An automatic dewpoint meter for the determination of condensable vapors. *Rev. Scient. Instruments*, 19: 16-23, 1948.

⁷ LESTER, W., ROBERTSON, O. H., PUCK, T. T., WISE, H. and SMITH, M. The rate of bactericidal action of triethylene glycol vapor on microorganisms dispersed into the air in small droplets. *Am. J. Hyg.*, to be published.

⁸ ROBERTSON, O. H., LESTER, W. and DUNKLIN, E. Unpublished experiments.

than was formerly thought to be the case.* It has not been found possible, however, to sterilize the air of inhabited rooms. Numerous tests under a variety of conditions have shown that the air-borne bacterial population can be reduced by not more than 70 to 75 per cent and the rate of killing is much slower than in the case of atomized bacterial suspensions. Investigation of dust-borne bacteria (non-pathogens with rare exceptions) indicates that the reason for their relative insensitivity to the lethal effect of triethylene glycol vapor lies in the physical state of the bacterial particle which obviously differs from that of the glycol-sensitive micro-organisms desiccated under laboratory conditions.

The utilization of glycol vapor for purposes of aerial disinfection involves a number of considerations which may be outlined briefly as follows: since triethylene glycol has a very low vapor pressure (boiling point is 550°F.) heat is essential for vaporization. However, the temperature which can be employed for this purpose is limited by the fact that this glycol begins to decompose at temperatures far below its boiling point. These properties of triethylene glycol introduce very definite requirements for the design of vaporizers. In order to disperse sufficient glycol into the air extended evaporating surfaces must be employed. Heating of the pool or reservoir of glycol should be avoided. Certain glycol vaporizers commercially available embody these principles, others do not.

Continuous dispersion of the glycol vapor into the treated space is essential because of the constant loss of vapor from the air, due to invisible condensation on all surfaces (including dust in the air) and the exchange

of air which goes on to some degree even when windows and doors are closed. This loss amounts to 70 to 90 per cent of the glycol vaporized.⁸ Hence in order to secure and maintain adequate concentrations of glycol in the air it is necessary to vaporize usually four to five times the amount of triethylene glycol calculated to produce the desired concentration in a given space. When air exchange in the room is increased by opening of doors and windows, the glycol requirement is even higher.

Air currents are necessary for uniform dispersion of glycol vapor throughout the treated space. In moderate-sized rooms of several thousand cu. feet the natural convection currents are usually adequate for this purpose. In larger spaces an electric fan or two depending on the size and shape of the space to be glycolized accomplishes the desired result. Air conditioning systems offer the most satisfactory means of glycol vapor distribution.

Maintenance of an adequate concentration of triethylene glycol vapor in the atmosphere offers the principal problem in the field of practical application. Until glycostats become available the only means of knowing whether sufficient glycol vapor is present, aside from chemical determination, is to produce a slight fog. The presence of a mist, best determined by the Tyndall effect (from a focused flashlight) does not necessarily indicate saturation of the air. A beam may be detectable at any concentration above 50 per cent saturation depending on the dustiness of the air. However, the occurrence of a Tyndall beam under ordinary conditions indicates the presence of a germicidal concentration. The optimum concentrations in terms of per cent saturation probably lie between 60 and 80 per cent.

Prior to its use in environments inhabited by human beings, prolonged tests (twelve to eighteen months) for chronic toxicity were carried out on monkeys and rats exposed continuously to atmospheres saturated with triethylene glycol vapor. In none of this large group of animals nor in

* Certain earlier studies,⁹ which indicated that dried bacteria were relatively unsuceptible to glycol vapor action at humidities below 30 per cent, were carried out before any means was available for measuring concentrations of triethylene glycol in the air. Subsequent developments have shown that the amounts of glycol used in those experiments which were calculated to saturate the air actually produced concentrations so low as to be almost negligible.

⁹ ROBERTSON, O. H. Sterilization of air with glycol vapors. Harvey Lecture Series, 38: 227-234, 1942-43.

others receiving oral doses many hundreds of times the amount they could absorb from inhalation were any deleterious effects observed either during life or in histologic sections of the organs following sacrifice at termination of the experiments.¹⁰ Subsequent to these tests thousands of individuals have resided in glycol-containing atmospheres, many of them continuously for months, without apparent disturbance. The presence of triethylene glycol vapor in the air offers no fire or explosive hazard.

Evidence of the effect of triethylene glycol vapor derived from practical application is as yet scanty. Tests of the lethal action of glycol vapor on pathogens demonstrable in the air have thus far been confined to observations on hemolytic streptococci. In hospital wards housing patients with streptococcal respiratory tract infections the dispersion of triethylene glycol vapor resulted in reduction of air-borne streptococci of approximately 70 per cent. However, when in addition to glycol, dust control measures (oiling of bedding and floors) were instituted, the reduction was increased to 95 per cent. These findings bring out the importance of dust suppression as an adjunct to the use of triethylene glycol vapor.¹¹

The few studies that have been reported on the clinical effects of employing glycol vapor for the prevention of air-borne infection are much more difficult to evaluate. The results of these experiments which were carried on in hospitals and military barracks vary from marked reduction of infections in the glycolized area¹² to inconclusive effects.¹³

¹⁰ ROBERTSON, O. H., LOSSLI, C. G., PUCK, T. T., LEMON, H. M., WISE, H. and LESTER, W. Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. *J. Pharmacol. & Exper. Therap.*, 91: 52-76, 1947.

¹¹ PUCK, T. T., HAMBURGER, M., ROBERTSON, O. H. and HURST, V. The effect of triethylene glycol vapor on air-borne beta hemolytic streptococci in hospital wards. II. The combined action of glycol vapor and dust control measures. *J. Infect. Dis.*, 76: 216-225, 1945.

¹² ROBERTSON, O. H. Disinfection of air by germicidal vapors and mists. *Am. J. Pub. Health*, 36: 390-391, 1946.

¹³ LOSSLI, C. G., SMITH, M. H. D., GAULD, R., ROBERTSON, O. H. and PUCK, T. T. Control of cross infections in infants' wards by the use of triethylenc glycol vapor. *Am. J. Pub. Health*, 37: 1385-1398, 1947.

Environmental conditions of the several tests differed markedly and it is quite likely that opportunities for the transmission of infection by routes other than the air likewise varied. This latter unknown, namely, the percentage of cases of the various diseases of the respiratory tract that are air-borne makes the evaluation of any control measure most difficult. In environments such as hospital wards adequately controlled tests of the effect of aerial disinfection on the incidence of diseases acquired by way of the respiratory tract must include rigid enforcement of ward technics intended to reduce the possibility of channels of infection other than through the air.

From the foregoing summary it is apparent that the usefulness of triethylene glycol vapor as a means of protection against respiratory infection remains to be determined. However, the fact that this vapor has been shown to be a potent aerial disinfectant, at least for freshly dispersed pathogens, indicates the worthwhileness of more clinical trials in a variety of environments. The kind of control employed in such tests will of necessity vary with the particular environment and will have to be planned for each type of population under study. It is only through an accumulation of results from controlled experiments of this kind that an evaluation of the procedure will be possible.

In conclusion, reference should be made to the nationwide sale of glycol vaporizers. Two recent editorials in medical periodicals^{14,15} have dealt with this subject pointing out the unfortunate aspects of unrestrained exploitation of glycol vapors and the fact that the majority of the vaporizing devices on the market are completely unsatisfactory. A few mechanically sound and efficient vaporizers are being produced and it seems likely that some means of official certification of such apparatus will soon be available.

O. H. ROBERTSON, M.D.

¹⁴ Commercial exploitation of glycol vaporizers. *Am. J. Pub. Health*, 39: 222-224, 1949.

¹⁵ The sale of glycol vaporizers. *Cincinnati J. Med.*, April, 1949.

I. Electrophoretic, Nitrogen and Lipide Analyses of Plasma and Plasma Fractions of Healthy Young Men*

H. ROWLAND PEARSALL, M.D. and ALFRED CHANUTIN, Ph.D.

Charlottesville, Virginia

COHN and his associates recently introduced technics¹ for large scale fraction of plasma. This procedure (method VI) has many advantages due to the relative simplicity of the method; fractions may be obtained by varying pH, ionic strength and ethanol concentrations at low temperatures. Information concerning the protein components of the fractions separated by method VI are available only for pooled Red Cross plasmas.^{1,2}

In the present investigation this procedure was modified so that small amounts of human plasma could be fractionated into Fractions I, II + III, IV-1, IV-4 and V. Variations of the electrophoretic patterns and of the nitrogen and lipide contents of the plasma and the plasma fractions of healthy young men are presented and may serve as normal standards for studies in which fractionation procedures are utilized in the investigation of the plasma in diseased states.

METHODS

Approximately 50 ml. of blood were drawn before breakfast from thirty male students (twenty to thirty years of age); clotting was prevented with heparin. Each blood was centrifuged shortly after collection and the plasma was removed immediately. Approximately 4 to 5 ml. of plasma were needed for electrophoretic and chemical analyses and the remaining plasma (17 to 20 ml.) was fractionated by slight modifications of method VI¹ within a few hours.

The plasma was fractionated in a 100 ml., round bottom, Pyrex centrifuge tube. The ethanol (53.3 or 95 per cent) was measured from a Machlett autoburette which was connected by rubber tubing to a small reservoir immersed in a low temperature bath. The cold ethanol was added slowly with continuous stirring to the protein-containing solution which was maintained at low temperatures (0 to -5°). The pH and ionic strengths were adjusted essentially as previously described.¹ The ethanol was added before adjusting pH and ionic strength. The pH was determined on small volumes (0.3 ml.) of the ethanol-protein mixture with the aid of a microcup and a Beckman instrument.

The plasma was diluted (1:1) initially with sodium chloride solutions (ionic strength 0.14) containing about 4 ml. of phosphate buffer (pH 6.4, ionic strength 0.15). The addition of the buffer was essential for the maintenance of proper hydrogen ion concentrations in the precipitation of Fractions I and II + III. Shortly after precipitation each fraction was dissolved in saline and brought to 10 ml. in a volumetric flask. Aliquots were taken for electrophoretic nitrogen and lipide analyses.

The plasma and fraction solutions were dialyzed against a barbiturate buffer (pH 8.6, ionic strength 0.1). Electrophoresis was carried out in the Tiselius apparatus at 2° , the patterns being recorded by the method of Longworth.³ A microcell* with a capacity of 2 ml. was used to obtain the electrophoretic patterns. Electrophoresis was usually allowed to continue for ninety minutes with a current of 8 ma. Mobility calculations were based on the distance from the peak of salt effect (δ) to the peak of the

* Obtained from Pyrocell Co., N. Y.

* From the Biochemical Laboratory, University of Virginia Medical School, Charlottesville, Va. This work was made possible by a grant from the Office of Naval Research.

respective components. The areas of the ascending patterns were measured.

The total lipides of the plasma and fractions were extracted with hot acetone-absolute alcohol (1:1). Aliquots were analyzed for cholesterol according to the procedures of Sperry and

RESULTS

Electrophoresis. The percentage distributions of the protein components of plasmas and four fractions (I, II + III, IV-4 and V) together with typical ascending patterns are

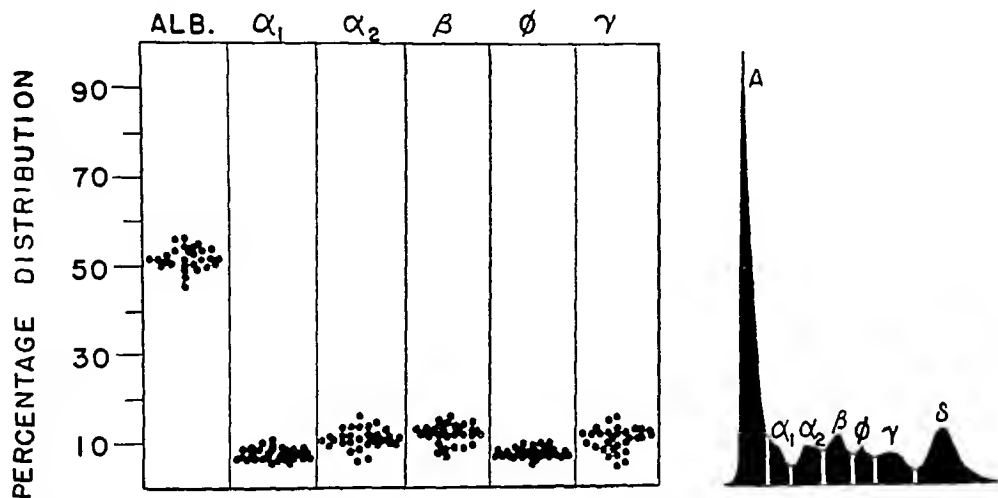


FIG. 1. Electrophoretic analyses of whole plasma; percentage distribution of protein components in plasma.

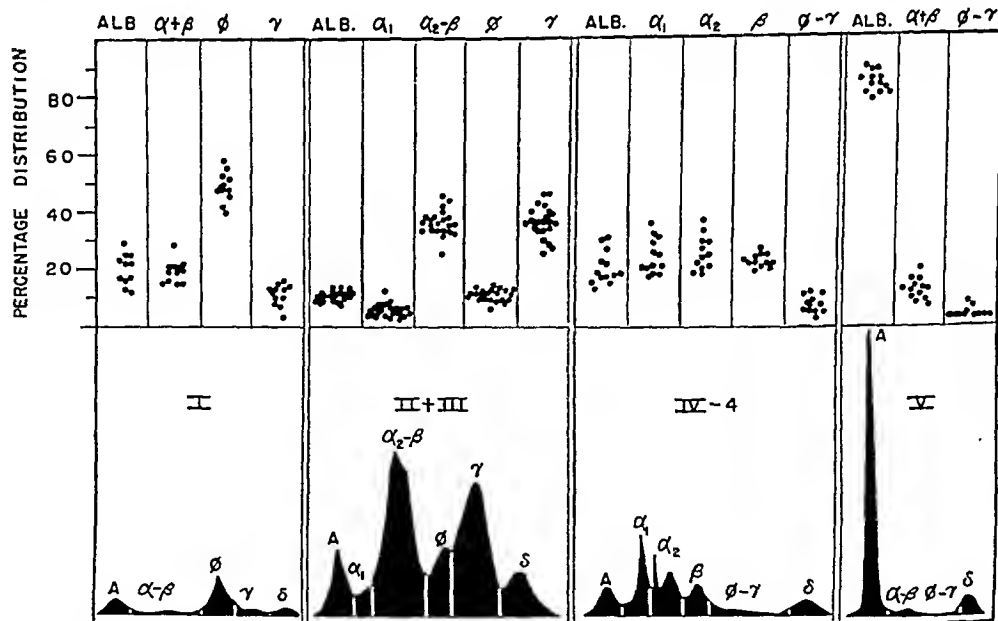


FIG. 2. Electrophoretic analyses of plasma fractions; percentage distribution of protein components in Fractions I, II + III, IV-4 and V.

Brand.⁴ Aliquots of the alcohol-acetone extract were evaporated to dryness, extracted with petroleum ether and the total lipid carbon was determined by the manometric technic of Van Slyke and Folch.⁵ Total nitrogen was determined by the micro-Kjeldahl procedure.

shown in Figures 1 and 2. Fraction IV-1 is omitted due to insufficient amounts for analyses. The variations in distribution of the various components are generally greater in the fractions than in whole plasma. The

mean values for percentage distribution of the protein components of the plasma and its fractions (Table I) are similar to those presented by the Harvard investigators.^{1,2} The small differences noted may be due to incomplete resolution in the microcell, age

of the plasma at the time of fractionation, sampling of individuals instead of pooled plasmas and slight differences in fractionation technic.

The mobilities of each component were determined for each fraction but were too

TABLE I
MEAN PERCENTAGE AREA DISTRIBUTIONS OF
ELECTROPHORETIC PATTERNS OF PLASMA
AND FOUR FRACTIONS

Electro- phoretic Component	Whole Plasma (30)* %	Fractions			
		I (12) %	II + III (22) %	IV-4 (13) %	V (13) %
Albumin	52	20	10	21	84
α_1	8	..	5	24	
α_2	11	19	36	26	13
β	12	23	
ϕ	7	49	13	6	4
γ	11	12	36		

* Figures in parentheses represent number of samples. All the fractions in twelve individual subjects were analyzed.

TABLE II
MEAN VALUES IN MG. OF THE CONTENTS OF PROTEIN
NITROGEN, LIPIDE CARBON AND CHOLESTEROL IN
EACH FRACTION PER 100 ML. PLASMA

Plasma	I	II + III	IV-1	IV-4	V	Total Contents in Fractions, %
Protein Nitrogen (30)*						
1083	87	258	40	124	477	986 (91)†
Total Lipide Carbon (30)						
491	44	254	48	74	42	462 (94)
Cholesterol (30)						
180	13‡	118	5‡	23‡	7‡	166 (92)
% Free Cholesterol						
26		29				

* Number of samples analyzed.

† Percentage recovery in fractions.

‡ Represents a limited number of determinations.

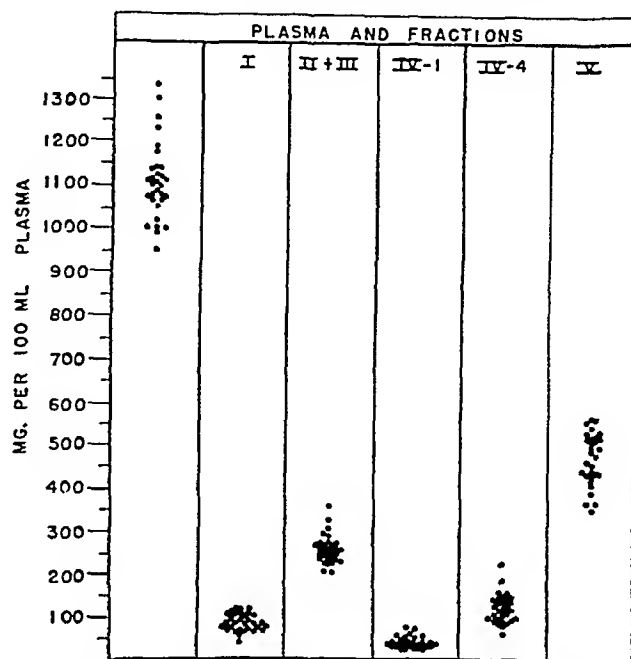


FIG. 3. Protein nitrogen contents of plasma and five plasma fractions.

variable for identifying the respective proteins. The relative positions of the components in the electrophoretic pattern were used as the means of identification.

Distribution of the nitrogen in plasma and five fractions of thirty subjects is shown in Figure 3. The greatest variations in individual values are seen in whole plasma and in Fraction v. The mean values for each fraction are shown in Table II. Approximately 75 per cent of the plasma protein is present in Fractions II + III and v. The distribution of the fractions in terms of nitrogen is similar to that noted by Cohn et al.¹

The lipide carbon values are shown graphically in Figure 4 and the mean values are given in Table II. More than one-half of the lipide carbon is present in Fraction II + III. According to the mean values there is an excellent recovery of lipide in the five fractions. However, an analysis of individual plasmas shows wide differences in the percentage recovery, varying from 75 to 118 per cent. The indi-

vidual lipid carbon contents of Fraction II + III constitute between 43 and 70 per cent of the total content of the plasma.

Detailed and mean data for cholesterol are presented in Figure 5 and Table II. Approximately 70 per cent of the total

obtainable from individual subjects,¹ by the low temperature-ethanol procedures developed by E. J. Cohn and associates for large scale fractionation of pooled plasmas.

Electrophoretic, nitrogen and lipid analyses of the plasma and five fractions (I,

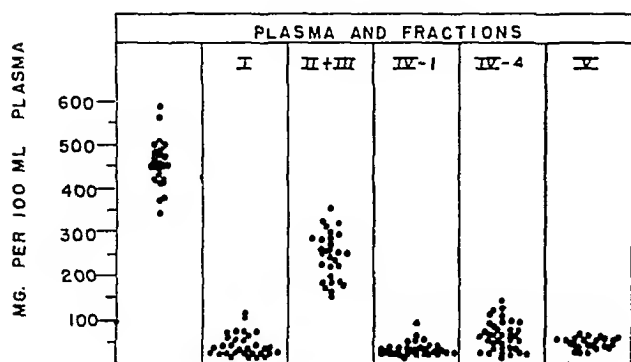


FIG. 4.

FIG. 4. Lipide carbon contents of plasma and five fractions.

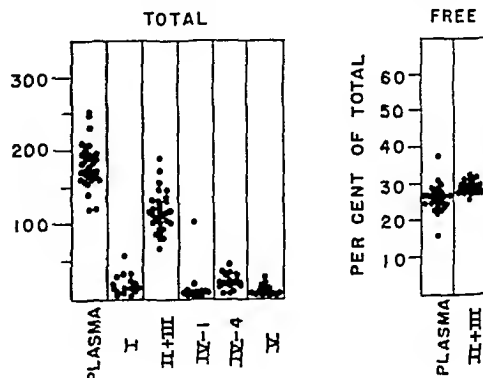


FIG. 5.

FIG. 5. Total cholesterol of plasma and five plasma fractions; and percentage free cholesterol in plasma and Fraction II + III.

cholesterol of the plasma is present in Fraction II + III. The marked constancy of the percentage of free cholesterol of Fraction II + III is worthy of note. The free cholesterol in the remaining fractions could not be determined accurately due to the small amounts present.

COMMENTS

According to Cohen and Thompson,⁶ the area distributions and mobilities of patterns obtained with the micro- and macrocells are in good agreement with each other. The microcell is essential in the present investigation because of the small amounts of available material. Fairly good agreement for the patterns obtained by the two types of cells has also been found in this laboratory. However, the mobility data are unsatisfactory due to the large variations for any given component. It is difficult to resolve satisfactorily the complexes in the ϕ and γ areas of Fractions IV-4 and V and in the α - β area of Fractions I and II + III.

SUMMARY

Methods are described for fractionating comparatively small volumes of plasma

II + III, IV-1, IV-4 and V) of healthy young men are presented.

Acknowledgments: The authors are indebted to Dr. Stephan Ludewig, Dr. E. C. Gjessing, Mr. J. P. Lewis, Mr. E. R. Berry and Miss B. A. Lentz for advice and technical assistance.

REFERENCES

1. COHN, E. J., STRONG, L. E., HUGHES, W. L., JR., MULFORD, D. J., ASHWORTH, J. N., MELIN, M. and TAYLOR, H. L. Preparation and properties of serum and plasma proteins. IV. A system for the separation into fractions of the protein and lipoprotein components of biological tissues and fluids. *J. Am. Chem. Soc.*, 68: 459, 1946.
2. ARMSTRONG, H. S., JR., BUDKA, M. J. E. and MORRISON, K. C. Preparation and properties of serum and plasma proteins. XI. Quantitative interpretation of electrophoretic schlieren diagrams of normal human plasma proteins. *J. Am. Chem. Soc.*, 69: 416, 1947.
3. LONGSWORTH, L. G. The observation of electrophoretic boundaries. *Ann. New York Acad. Sc.*, 39: 187, 1939.
4. SPERRY, W. M. and BRAND, F. C. The colorimetric determination of cholesterol. *J. Biol. Chem.*, 150: 315, 1943.
5. VAN SLYKE, D. D. and FOLCH, J. Manometric carbon determination. *J. Biol. Chem.*, 136: 509, 1940.
6. COHEN, P. P. and THOMPSON, F. L. A comparative study of micro- and macroelectrophoretic analysis of human and rat serum. *J. Lab. & Clin. Med.*, 33: 75, 1948.

II. Electrophoretic, Nitrogen and Lipide Analyses of Plasma and Plasma Fractions in Disease*

H. ROWLAND PEARSALL, M.D. and ALFRED CHANUTIN, Ph.D.

Charlottesville, Virginia

CHANGES in the distribution and properties of the plasma proteins noted during disease are of considerable interest to clinicians and investigators. In a recent review of the literature dealing with plasma proteins in disease Gutman¹ pointed out that distribution of these proteins is generally not specific for any one disease but is characterized by a decrease in albumin and an increase in various globulin components.

Most of the available information is based on electrophoretic studies of plasma and plasma fractions obtained with neutral salt precipitation. The inability to correlate the changes in plasma proteins with a specific disease detracts from the diagnostic value of plasma protein fractionation by present salting-out methods. The carefully controlled fractionation procedures of Cohn and associates² provide another approach to the study of this problem. Application of these techniques to relatively small volumes of dog,³ rat⁴ and goat⁵ plasmas reveal changes in the distribution of protein components after injury.

In a previous paper⁶ the plasma proteins of normal young men were fractionated by the low temperature-ethanol procedures and standards were established for the electrophoretic, nitrogen and lipide distributions of the plasma fractions. In this investigation these same procedures were applied to the plasmas of patients with a variety of diseases.

RESULTS

The plasmas and the plasma fractions of patients with multiple myeloma, hepatic disease, nephrotic syndrome, malignant hypertension, pneumonia and a variety of other diseases were studied.

Multiple Myeloma. The data in six cases of proven multiple myeloma are presented. Two of these patients had normal plasma nitrogen concentrations but hyperglobulinemia was present in all cases. (Fig. 1.) Most of the nitrogen values in Fractions I and II + III were elevated while the albumin contents (Fractions V) were all decreased. The protein contents of Fractions IV-1 and IV-4 were not affected. The lipidic carbon contents of the plasma and Fraction II + III were decreased except in one instance; the values for the remaining fractions were normal. (Fig. 1.) The total cholesterol contents were somewhat decreased and the percentage-free cholesterol was not appreciably affected.

The electrophoretic patterns for the plasma and four fractions of Patient O. H. are shown in Figure 2; pertinent patterns are shown for the remaining five patients. (Fig. 3.) The abnormal protein component ("M") has the mobility of gamma globulin in five of the six patients and has the solubility characteristics of gamma globulin in the fractionation procedure. It is the chief protein in Fraction II + III.

The electrophoretic analysis of the protein components of the plasma and Fraction

* From the Biochemical Laboratory, University of Virginia Medical School, Charlottesville, Va. This work was made possible by a grant from the Office of Naval Research.

II + III of all patients are graphically presented in Figure 4. It will be noted that the gamma globulin component was increased in five patients; two determinations taken

components of Fraction IV-4 and V of multiple myeloma plasmas was normal. The distribution and properties of component M were not uniform. In patient

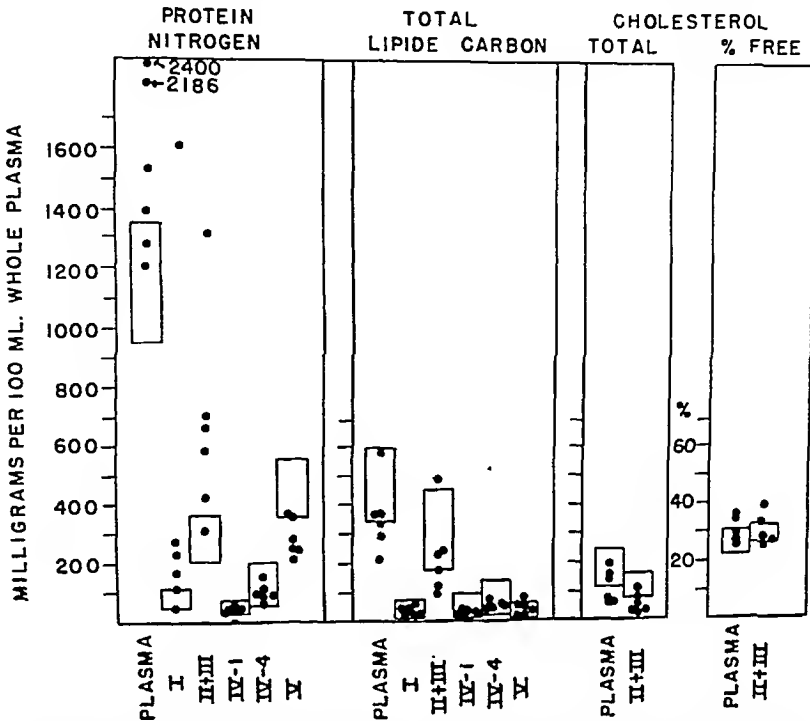


FIG. 1. Protein nitrogen, lipid carbon and cholesterol contents in the blood plasma and fractions of six cases of multiple myeloma. The rectangles in this and other figures represent the limit of variations in normal subjects.

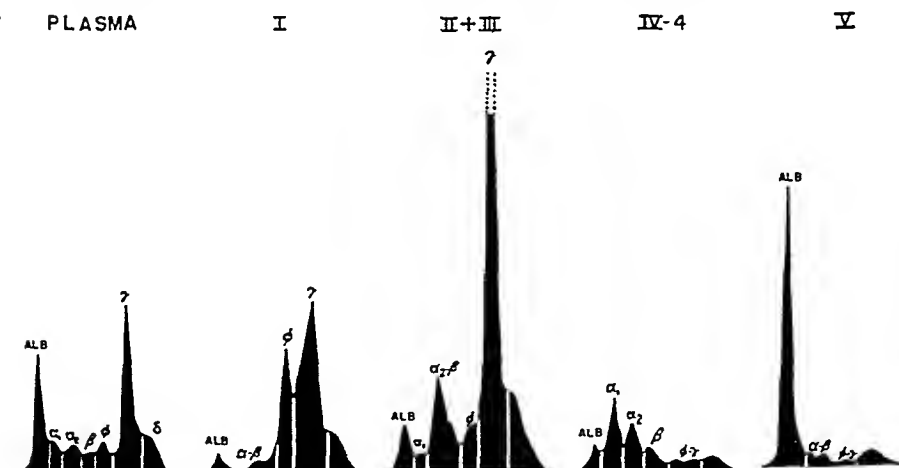


FIG. 2. Electrophoretic patterns of plasma and four fractions of a case of multiple myeloma; patient O. H.

at an interval of one month for Patient C. H. were elevated in the fibrinogen range in both the plasma and Fraction II + III. The α_2 - β area was decreased in Fraction II + III in all cases. Distribution of the

O. H. (Fig. 2) most of the abnormal protein was present in Fraction II + III, but an appreciable amount was also present in Fraction I. Although the mobility of the abnormal protein of the plasma of G. H.

(Fig. 3) was in the γ range, 72 per cent of the total plasma nitrogen (2.4 gr. per cent) was present in Fraction I; a saline solution of this fraction solidified on standing. It was

from this patient was unusually viscous; this property was not observed after the patient was treated with stilbamidine for a month. A viscous protein was also described

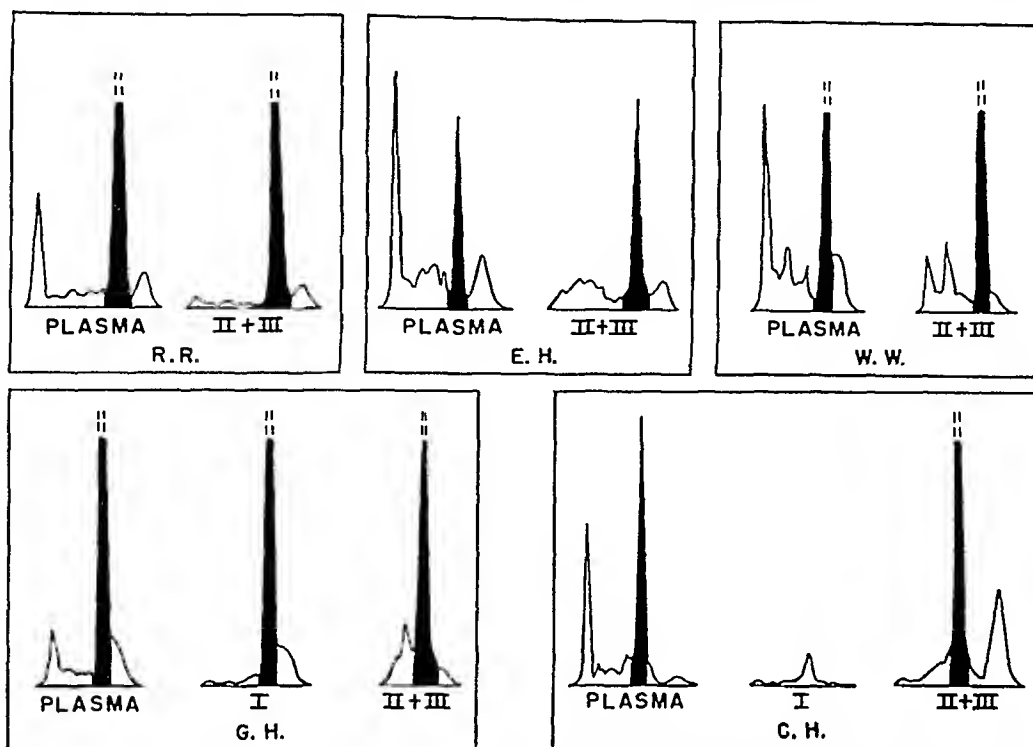


FIG. 3. Electrophoretic patterns of the plasma and Fractions I and II + III of five cases of multiple myeloma. The solid portion of the pattern represents the "M" component.

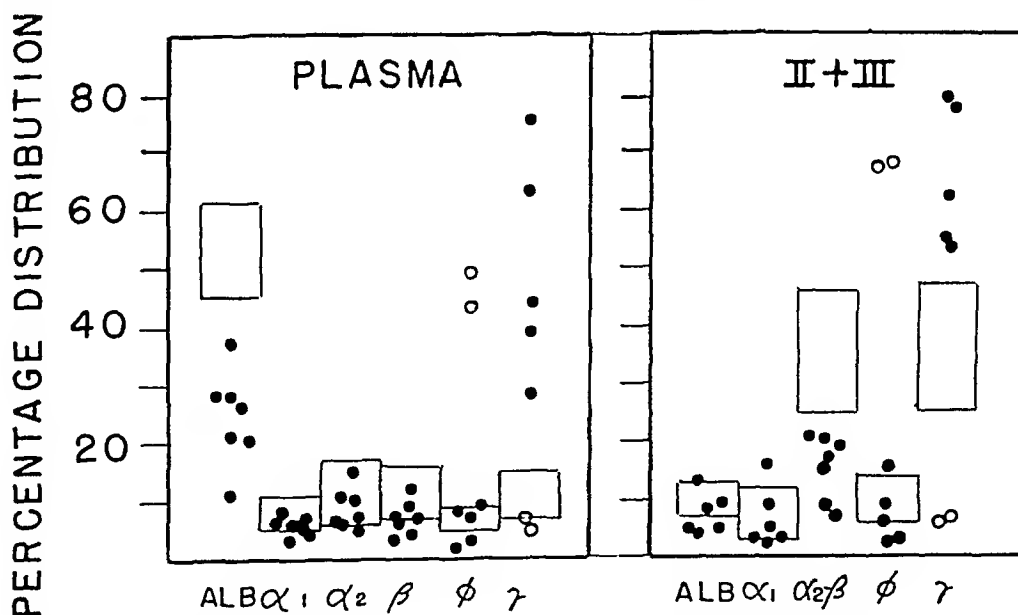


FIG. 4. Analyses of the electrophoretic patterns of plasma and Fraction II + III of six cases of multiple myeloma. The open circles designate the results obtained for patient C. H.

noted that the M component of the plasma of C. H. (Fig. 3) appeared to have the mobility of fibrinogen but on fractionation was absent in Fraction I. A solution of Fraction II + III of the first plasma obtained

by Shapiro et al.⁷ It is improbable that this therapy was responsible for the change in physical property.

Liver Disease. In this group five cases of hepatitis of virus etiology and five of

Laennec cirrhosis are discussed. The results are shown in Figures 5 and 6.

Despite the normal values for plasma nitrogen (Fig. 5) these patients exhibit hyperglobulinemia as evidenced by the elevated values in Fractions I and II + III

distribution of the components of the electrophoretic patterns tended to return to the normal ranges. No demonstrable differences in the electrophoretic patterns were seen at widely varying intervals in two of the cirrhotics studied.

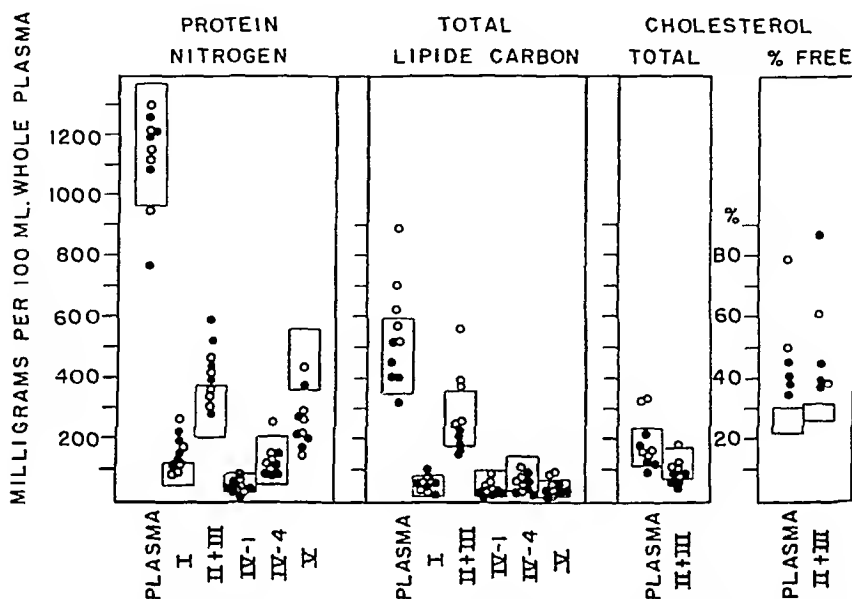


FIG. 5. Protein nitrogen, lipid carbon and cholesterol contents in the blood plasma and fractions of ten cases of liver disease; O = hepatitis; ● = cirrhosis.

and decreases in albumin (Fraction v). The lipid carbon contents are not appreciably affected. The total cholesterol of Fraction II + III of the cirrhotics are below normal. Liver damage is reflected in the increased values for the percentage-free cholesterol, particularly in the hepatitis patients.

Electrophoretic patterns of plasma and Fraction II + III from two cirrhotic patients in the terminal stage are shown in Figure 6. The distribution and concentration of the protein components are quite different under conditions which are clinically identical. Most of the patients with cirrhosis have electrophoretic patterns similar to Case II. The electrophoretic patterns of hepatitis plasma and Fraction II + III are qualitatively similar to those of cirrhosis; the γ globulin area tends to be smaller in the hepatitis patients.

In one patient with hepatitis who showed clinical improvement the lipid and nitrogen contents of the plasma and fractions and

Nephrotic Syndrome. Studies on five patients with marked albuminuria, edema, hypo-albuminemia and hypercholesterolemia are presented. In two cases patients were studied at intervals during treatment. The data are summarized in Figures 7 and 8.

The very low nitrogen content of Fraction v and marked elevation of lipid carbon and cholesterol contents of the plasma and Fraction II + III are the outstanding chemical changes noted in Figure 7. Two plasma nitrogen concentrations of a patient treated for a long period are in the control range but the albumin contents remain subnormal. Electrophoretic patterns of the plasma and the fractions of two patients are shown in Figure 8. The changes seen in the plasma of subject V. A., a twelve year old girl with a typical nephrotic syndrome, were similar to those described by other investigators. The α_2 - β components of Fractions II + III and v were increased and the

albumin component of Fraction v was markedly decreased. The nephrotic syndrome of patient S. P., a forty-five year old male, was complicated by psoriasis and atrophic arthritis. In this case the α_2 component was prominent in all patterns except

the first two weeks. The plasma and Fraction II + III pattern (Fig. 10) on the ninth day after the onset of illness was unusual due to the marked increases in the α globulins and fibrinogen. On the sixteenth day the patient showed definite signs of im-

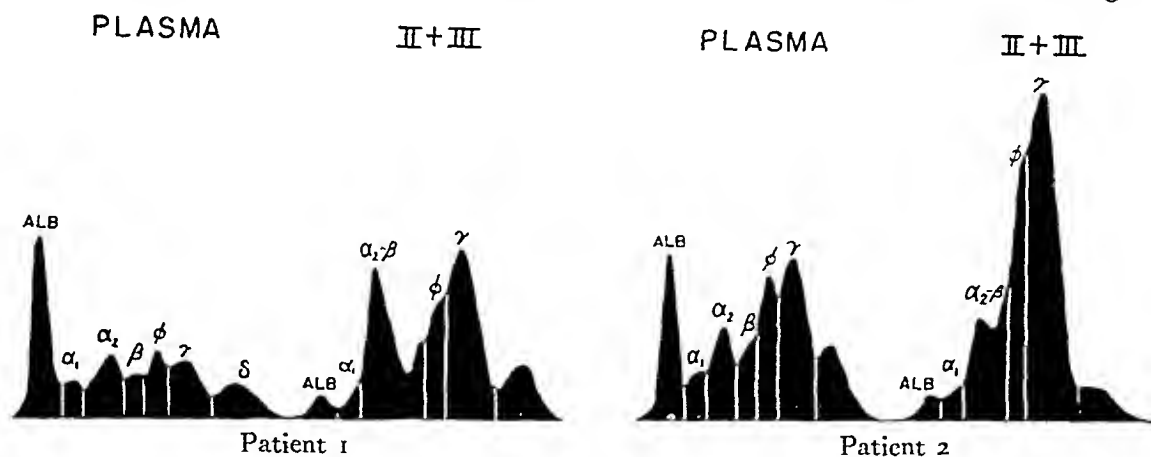


FIG. 6. Electrophoretic patterns of two cirrhotic patients in the terminal stage.

Fraction I; the fibrinogen was increased in the plasma and Fractions I and II + III; the β component was present in small amounts.

The electrophoretic analyses of the plasmas of all patients showed a marked decrease of albumin and an elevation of the α_2 , β and ϕ components. The α_2 - β areas of Fraction II + III were consistently increased.

Malignant Hypertension. The results obtained in four patients in various phases of this disease are given. (Fig. 9.) The outstanding changes in the chemical analyses were as follows: increases in the nitrogen contents of Fraction I and II + III and decreases in Fraction v; decreases of total cholesterol of Fraction II + III in three of the four patients and elevation in the percentage-free cholesterol of the plasma and Fraction II + III. No striking change was observed in the electrophoretic analyses except for a decrease in the albumin component of the plasma.

Pneumonia. The patients in this group represent two severely ill patients due to type 33 pneumococcus (J. W.) and tularemia (H. D.) and three moderately severe pneumonias of unknown etiology (C. M., A. P. and M. G.).

Case I (J. W.) ran a particularly stormy course with continuous high fever during

provement. The patient was discharged on the twenty-third day and was back at work on the forty-third day but the electrophoretic patterns, pulmonary x-ray and physical findings at this time had not yet returned to

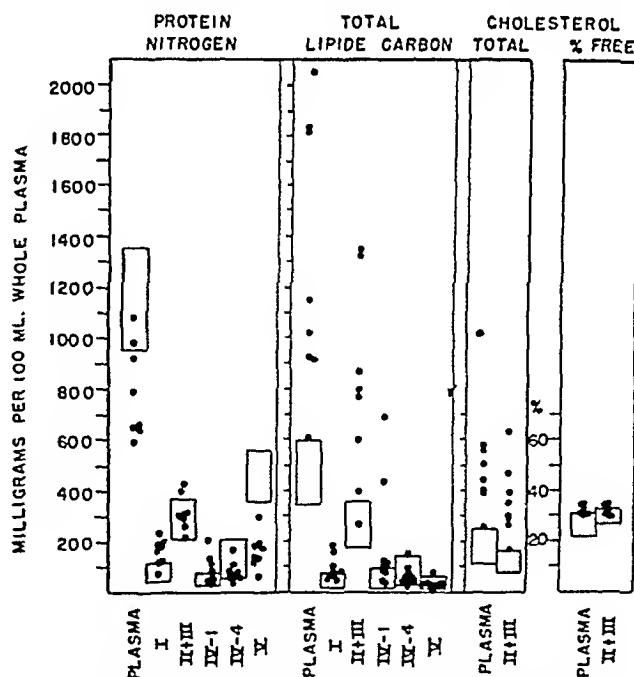


FIG. 7. Protein nitrogen, lipid carbon and cholesterol contents in the blood plasma and fractions of five cases with the nephrotic syndrome.

normal. During recovery the electrophoretic patterns were characterized by increases in the γ globulins and albumin and decreases in α globulin and fibrinogen.

The changes in the nitrogen distribution in Case I are noteworthy since the albumin content decreased and the γ globulin-rich Fraction II + III increased at about the

however, changed from subnormal to normal values, with recovery.

The tularemic pneumonia patient (H. D.) was very ill when admitted to the hospital

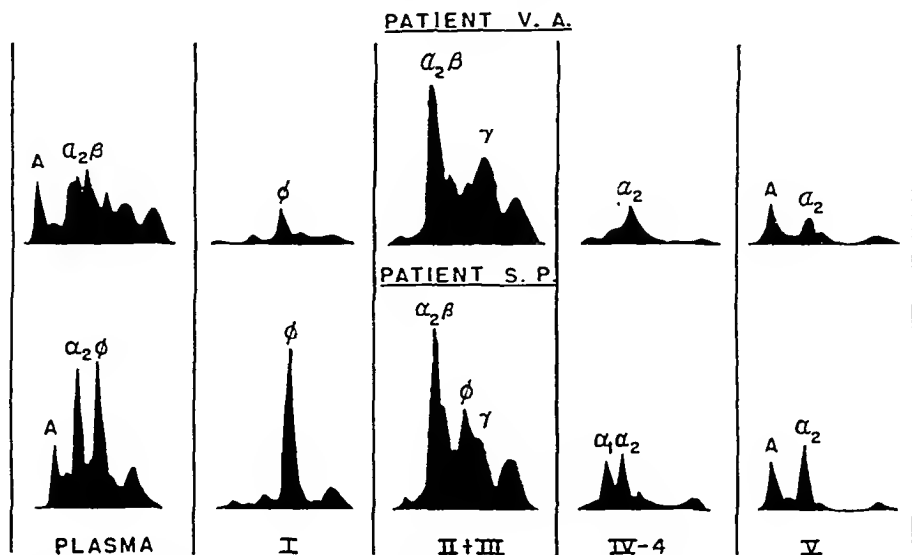


FIG. 8. Electrophoretic patterns of the plasma and four fractions of two cases with the nephrotic syndrome.

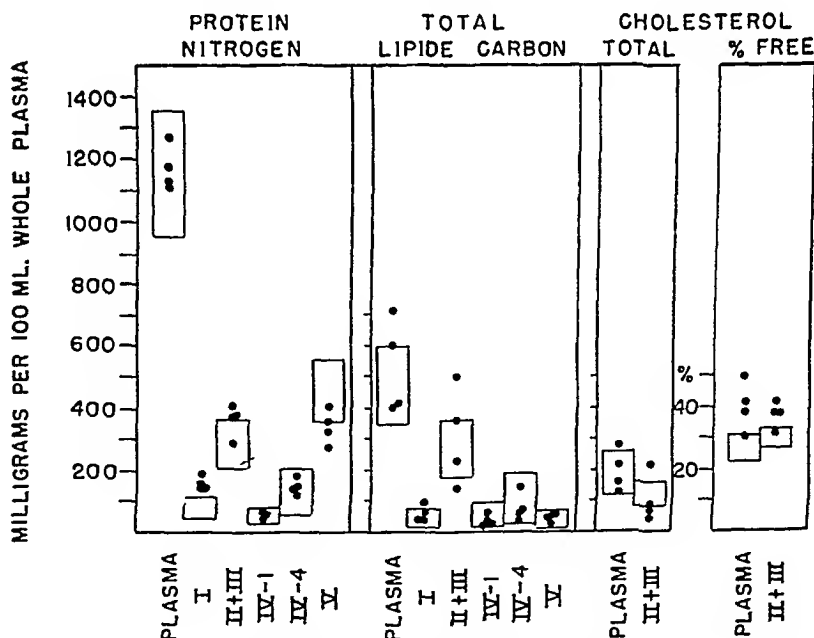


FIG. 9. Protein nitrogen, lipid carbon and cholesterol contents in the blood plasma and fractions of four cases of malignant hypertension.

time of clinical improvement. (Table I.) After this time values for the various fractions tended to return to normal. The changes in the lipid carbon were not striking or consistent. The cholesterol contents,

on the ninth day of his illness. At this time the nitrogen contents of the plasma and its fractions, particularly Fraction V, were decreased; the cholesterol contents were subnormal and the percentage-free cho-

lesterol was elevated in the plasma and Fraction II + III. (Table I.) At the time of definite improvement (the twenty-eighth day) the nitrogen content of the plasma was in the normal range due chiefly to increases in the fibrinogen, γ globulin and albumin

patterns of the plasma and fractions were not particularly striking in these three patients.

Miscellaneous Diseases. The following diseases were studied: lymphopathia venereum; heart failure (six cases); acute

TABLE I
NITROGEN, LIPIDE CARBON AND CHOLESTEROL CONTENTS PER 100 ML. OF PLASMA AND PLASMA FRACTIONS
IN FIVE CASES OF PNEUMONIA AT VARYING INTERVALS DURING THE ILLNESS

Day of Illness	Protein Nitrogen						Total Lipide Carbon						Cholesterol	
	Plasma	I	II + III	IV-1	IV-4	V	Plasma	I	II + III	IV-1	IV-4	V	Plasma	II + III
Case I, J. W., a male, aged 31														
9	903	175	212	22	152	200	378	82	139	21	41	41	81	41
16	1260	193	526	22	302	119	229	94	109	22	80	47	98	37
23	1330	221	516	30	199	279	394	128	128	42	134	43	139	34
43	1232	133	403	58	129	460	432	95	164	29	98	71	158	69
Case II, H. D., a male, aged 27														
10	725	64	216	33	70	252	474	38	326	40	53	34	89 (57)*	68 (63)*
17	808	75	293	26	99	244	418	36	290	19	50	23	107 (49)	87 (42)
28	1350	179	518	18	117	334	470	38	249	17	78	44	208 (35)	136 (34)
Case III, C. M., a male, aged 44														
5	974	223	200	87	179	274	523	33	169	38	63	41	72 (46)	49 (40)
7	966	160	237	55	161	308	453	36	174	48	35	36	95 (31)	67 (36)
Case IV, A. P., a male, aged 29														
5	974	144	284	45	143	296	389	42	218	40	51	18	79 (40)	58 (44)
12	1192	207	403	50	86	334	467	60	219	35	35	29	116 (30)	91 (29)
Case V, M. G., a female, aged 19														
7	897	150	281	34	91	281	366	79	154	28	89	37	102 (38)	44 (34)
14	1040	120	360	26	108	318	543	183	303	59	50	54	168 (33)	135 (30)

* Figures in parentheses represent the percentage-free cholesterol.

in Fractions I, II + III and V, respectively. The lipide carbon contents were not appreciably affected during the illness. The cholesterol contents rose and the percentage-free cholesterol decreased to normal limits.

In the three remaining patients with pneumonia the pertinent chemical changes (Table I) during recovery were similar in general to those observed in patients J. W. and H. D. The changes in electrophoretic

nephritis; pernicious anemia; sickle cell anemia; periarteritis nodosa; arsenic poisoning; early syphilis before and after treatment (two cases); Hodgkin's disease before and after treatment with nitrogen mustards (three cases) and rheumatic fever (two cases). The electrophoretic patterns of the plasma in these patients were similar to those obtained by other investigators. The patterns of Fraction II + III usually reflect

the outstanding changes in the globulin components of the plasma. Generally there is an increase in the nitrogen content of Fraction II + III and a decrease of Fraction v. No characteristic changes in the lipid values were observed.

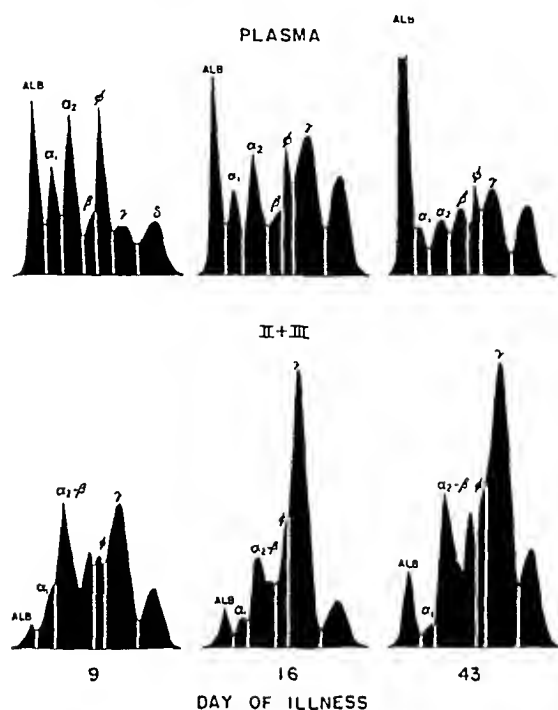


FIG. 10. Electrophoretic patterns of plasma and Fraction II + III of a case of pneumococcal pneumonia at varying intervals during the disease; patient 1.

COMMENTS

The literature concerned with the electrophoresis of plasma in disease was reviewed by Stern and Reiner,⁸ Luetseher⁹ and Gutman.¹ It is generally agreed that this procedure is of limited value as a diagnostic test. Corroborative evidence is presented in this paper which shows a lack of specificity of the electrophoretic pattern of plasma in most diseases.

The nitrogen, lipid carbon and cholesterol contents of each of the five plasma fractions could be determined in relatively small volumes of plasma. In most diseases the nitrogen content of the fibrinogen-rich Fraction I is elevated due chiefly to an increase in fibrinogen. The protein content of Fraction II + III is usually increased except in nephrotic cases. The nitrogen of the

albumin-rich Fraction v is depressed in all diseases of moderate or marked severity and this is particularly striking in nephrosis and liver disorders. The increased lipid carbon contents of the plasmas of patients with nephrosis and hepatitis are usually reflected in Fraction II + III. It is striking that the ratio between the cholesterol contents of total plasma and Fraction II + III remains within the normal range⁶ in the diseases studied. The values for the percentage-free cholesterol are approximately the same for plasma and Fraction II + III.

Electrophoretic analyses of the plasma fractions yield more detailed information concerning the distribution of proteins than is observed in the plasma. Fraction II + III usually shows the greatest qualitative changes in disease due to variations in the distribution of the α_2 - β and γ globulins. The remaining fractions do not show appreciable variations in the percentage distribution of the components. At present it is impossible to assess the significance of the percentage distribution of the components in these fractions. Increases in a given component may indicate the presence of an abnormal protein or an increased content of the normally-occurring protein. In order to appreciate the changes seen in plasma fractions it will be necessary to separate these components and determine their physical and chemical characteristics. Such studies would be particularly applicable to plasmas of patients with the nephrotic syndrome, liver diseases, multiple myeloma and severe infections.

SUMMARY AND CONCLUSIONS

The plasmas of patients with multiple myeloma, liver disease, nephrotic syndrome, malignant hypertension, pneumonia and a variety of other diseases were separated quantitatively into five fractions (I, II + III, IV-1, IV-4 and v) by the ethanol-low temperature, low salt procedures. These plasma and fractions were analyzed electrophoretically and their nitrogen, lipid carbon and cholesterol contents were determined.

The abnormal protein component (M)

of multiple myeloma plasma is usually present in Fraction II + III but may also be found in Fraction I. The mobility characteristics of this protein in plasma do not necessarily determine the fraction in which the M component is present.

The degree of alteration in the plasma protein patterns is, in general, determined by the severity of the disease. The abnormalities in the distribution of the protein components noted, particularly in Fraction II + III, appear to be non-specific. Significant changes in the nitrogen and lipid distributions may be seen in Fractions I, II + III or V.

Acknowledgments: The authors are indebted to Mr. J. P. Lewis, Mr. E. R. Berry, Miss B. A. Lentz and Miss F. L. Jones for technical assistance.

REFERENCES

1. GUTMAN, A. B. The plasma proteins in disease. *Advances in Protein Chemistry*. Vol. 4, p. 155. New York. Academic Press. 1948.
2. COHN, E. J., STRONG, L. E., HUGHES, W. L., JR., MULFORD, D. J., ASHWORTH, J. N., MELIN, M. and TAYLOR, H. L. Preparation and properties of serum and plasma proteins. IV. A system for the separation into fractions of the protein and lipoprotein components of biological tissues and fluids. *J. Am. Chem. Soc.*, 68: 459, 1946.
3. GJESSING, E. C., LUDEWIG, S. and CHANUTIN, A. Fractionation, electrophoresis, and chemical studies of proteins in sera of control and injured dogs. *J. Biol. Chem.*, 170: 551, 1947.
4. GJESSING, E. C. and CHANUTIN, A. An electrophoretic study of plasma and plasma fractions of normal and injured rats. *J. Biol. Chem.*, 169: 657, 1947.
5. GJESSING, E. C., LUDEWIG, S. and CHANUTIN, A. Fractionation, electrophoresis, and chemical studies of proteins in sera of control and injured goats. *J. Biol. Chem.*, 174: 683, 1948.
6. PEARSALL, H. R. and CHANUTIN, A. Electrophoretic, nitrogen, and lipid analyses of plasma and plasma fractions of healthy young men. *Am. J. Med.*, 7: 297, 1949.
7. SHAPIRO, S., ROSS, V. and MOORE, D. H. A viscous protein obtained in large amount from the serum of a patient with multiple myeloma. *J. Clin. Investigation*, 22: 137, 1943.
8. STERN, K. G. and REINER, M. Electrophoresis in medicine. *Yale J. Biol. & Med.*, 19: 67, 1946.
9. LUETSCHER, J. A., JR. Biological and medical applications of electrophoresis. *Physiol. Rev.*, 27: 621, 1947.

A Spontaneously Precipitable Protein in Human Sera, with Particular Reference to the Diagnosis of Polyarteritis Nodosa*

HAROLD LEPOW, M.D., LEO RUBENSTEIN, M.D., FANYA WOLL and HARRY GREISMAN, M.D.
New York, New York

DURING routine analysis of sera in the chemistry laboratory one of us (F. W.) noted a precipitate in a certain serum after cooling for twenty-four hours at 4°C. On repeated examination of the same serum under similar conditions the same result was obtained. The clinical diagnosis in this case (Case I) was polyarteritis nodosa, subsequently proved by postmortem examination. All sera analyzed in the laboratory thereafter were examined for this precipitate. A second case (Case II) was subsequently found showing the same type of precipitate. The clinical diagnosis here again was polyarteritis nodosa, also proved by postmortem examination.

On further analyses of sera three additional cases were found in which the clinical diagnoses were portal cirrhosis of the liver (Case III), subacute bacterial endocarditis (Case IV) and septicemia (Case V). The patient with portal cirrhosis died but permission for postmortem examination was not obtained. The remaining two patients have been under follow-up observation. A sixth case was observed recently in which the clinical diagnosis was polyarteritis nodosa, proved by biopsy. A detailed study of the serum of this last patient was undertaken in order to determine the nature of the precipitate by means of electrophoretic analysis.

CASE REPORTS

CASE I. F. C., a fifty-four year old white male, was admitted to Lincoln Hospital in a

semicomatose condition on January 17, 1947. The diagnosis of polyarteritis nodosa was made because of the presence of fever, leukocytosis, changes in the ocular fundus, hematuria, azotemia, anuria, peripheral neuritis, purpura, gangrene and convulsive seizures. No eosinophilia was detected. Serum total proteins rose from 4.6 Gm. per cent (albumin/globulin ratio of 2.4/2.2) to 6.8 Gm. per cent (albumin/globulin ratio of 3.6/3.2) and 7.1 Gm. per cent (albumin/globulin ratio of 4.1/3.0), with the cephalin flocculation at first negative, then plus-minus and then 3 plus before death on April 7, 1947, the eighty-eighth hospital day. Blood non-protein nitrogen reached 114 mg. per cent. Postmortem examination confirmed the clinical diagnosis. Lesions of polyarteritis nodosa were found in the kidneys, pancreas, heart, lungs, skin, muscles, seminal vesicles, mediastinal vessels and liver.

This was the first case in which the presence of a spontaneously precipitable protein was noted.

CASE II. M. L., a thirty-six year old Negro male, was first admitted to Lincoln Hospital on May 25, 1945, because of migrating joint pains of three days' duration. Findings suggested the diagnosis of acute rheumatic fever with polyarthritis. Response to salicylate therapy was so good that the patient left the hospital against advice after twenty days.

The second admission was on June 6, 1947, because of weakness, fever and pain in the right wrist. A diagnosis of acute exacerbation of rheumatic polyarthritis was proposed and the patient was again given salicylates. Shortly afterward hypertension, proteinuria and hematuria appeared. On July 2, 1947, after the onset

* From the Medical Service and the Laboratory, Lincoln Hospital, Department of Hospitals, New York, N. Y.

of spiking temperature and generalized edema, polyarteritis nodosa was first suspected. It was at this time that the laboratory demonstrated the appearance of a spontaneously precipitable protein in a specimen of venous blood withdrawn for analysis. Biopsy of gastrocnemius muscle was negative for evidence of polyarteritis nodosa. There was no eosinophilia.

Total serum protein was 5.3 Gm. per cent, with albumin/globulin ratio of 2.9/2.4; cephalin flocculation was negative. Later the total protein was 5.6 Gm. per cent, with albumin/globulin ratio of 3.1/2.5; the cephalin flocculation was plus-minus. Blood non-protein nitrogen was 112 and 132 mg. per cent. A second biopsy of gastrocnemius, July 17, 1947, showed hyalinized blood vessels.

In spite of the development of a wrist drop and other evidence of peripheral neuritis, as well as of pericarditis, the patient left the hospital against advice on July 29, 1947. Post-mortem confirmation of polyarteritis nodosa was made fortuitously because an assistant medical examiner had to be called when the patient died at home ten days later unattended by a physician. The findings of the assistant medical examiner indicated the presence of polyarteritis nodosa of the intestine, kidneys, lungs and testicles, with bilateral hydrothorax, pericarditis and ascites.

In this case there was a history of taking sulfonamides for scarlet fever four weeks before the first admission. A spontaneously precipitable protein appeared before biopsy confirmation. It appeared in the absence of eosinophilia. Azotemia was present and the cephalin flocculation was becoming increasingly positive. The first diagnosis of polyarteritis nodosa was made less than one month after the second admission.

CASE III. E. O., a forty-two year old white alcoholic female, admitted to Lincoln Hospital in a semicoma on March 8, 1947, presented the typical picture of cirrhosis of the liver. Total protein was 6.4 Gm. per cent. Later examinations showed total protein 6.0 Gm. per cent, with albumin/globulin ratio of 2.9/3.1 and total protein 6.1 Gm. per cent, with albumin/globulin ratio of 2.9/3.2. Cephalin flocculation was 4 plus. Blood urea nitrogen was 67 and 69 mg. per cent, with a non-protein nitrogen of 132 and 102 mg. per cent. The patient was

given penicillin for right lower lobe pneumonia. She developed bilateral wrist drop and signs of peripheral neuritis in spite of massive vitamin therapy and she died suddenly after the onset of extreme dyspnea on April 5, 1947. Post-mortem examination was not permitted.

In this case a spontaneously precipitable protein was present when there was a reversal of the albumin/globulin ratio, 4 plus cephalin flocculation and azotemia.

CASE IV. H. P., a white female, was twenty-six years old when she was first admitted to Lincoln Hospital as an obstetric patient on March 31, 1940. She was also treated with sulfonamides for acute pyelitis and acute mastitis in June, 1940, and in July, 1940 for an ischiorectal abscess. In May, 1947, aged thirty-three, she was admitted for spontaneous sub-arachnoid hemorrhage. The presence of a palpable spleen, a systolic murmur and clubbing of the fingers, even in the absence of petechiae and of positive blood culture, suggested sub-acute bacterial endocarditis. Laboratory studies included: total protein 7.9 Gm. per cent, with an albumin/globulin ratio of 3.5/4.4; total protein 6.9 Gm. per cent, with an albumin/globulin ratio of 3.5/3.4; total protein 6.9 with an albumin/globulin ratio of 3.4/3.5. Cephalin flocculation tests were 3 plus and 4 plus. She left against advice after five weeks. She continued to run low grade fever at home in spite of daily injections of penicillin in oil and beeswax given by her private physician.

She re-entered the hospital on August 14, 1947, because of continuous headache, sleeplessness and fleeting dull aches in the leg muscles, together with paresthesias. Biopsy of skin and of gastrocnemius muscle was negative for polyarteritis nodosa. Enlarged heart, splenomegaly, systolic murmur and clubbing were still present. Diagnosis of subacute bacterial endocarditis was confirmed by the finding of three successive blood cultures positive for *Streptococcus viridans* one week after admission. She received appropriate treatment with penicillin and developed petechiae in the course of therapy. On August 27, 1947, a spontaneously precipitable protein was noted in a specimen of blood taken for analysis. Total protein was 6.6 Gm. per cent, with albumin/globulin ratio of 3.8/2.8. After removal of the precipitate the same specimen showed a total protein of 6.6 Gm.

per cent, with albumin/globulin ratio of 3.0/3.6. Cephalin flocculation at this time was 4 plus. On a later specimen total protein was 7.3 Gm. per cent and the albumin/globulin ratio was 3.6/3.7, with 4 plus cephalin flocculation. The clinical diagnosis was congenital heart disease, probably interventricular septum defect, in conjunction with subacute bacterial endocarditis. Total penicillin administered in the forty-one days from August 23, 1947, to October 3, 1947, when she left against advice, was 82 million units.

On re-admission from October 5 to October 17, 1947, for weakness, headaches, paresthesias and unconsciousness, she received an additional 26 million units of penicillin. Angiocardiography performed at another hospital later that month confirmed the clinical diagnosis of interventricular septum defect. She is being treated at home by a staff member, through whose cooperation follow-up examinations and blood studies have been made possible. The clinical condition is good and apparently the subacute bacterial endocarditis has been cured. A spontaneously precipitable protein is present in some examinations and absent in others.

In this patient a spontaneously precipitable protein appeared when the total protein was relatively high, when the albumin/globulin ratio was reversed and when 4 plus cephalin flocculation was present.

CASE V. W. W., a fifty-eight year old Negro male, was admitted to Lincoln Hospital on January 12, 1947, acutely ill with bronchopneumonia and rheumatoid arthritis. Eosinophilia of 15 per cent and the finding of a tarry stool two days later led to suspicion of polyarteritis nodosa, made stronger by the appearance later that day of a urea frost and a blood non-protein nitrogen of 198 mg. per cent. Muscle biopsy, however, was negative. Acidotic breathing, massive edema and ascites also appeared. Total protein was 5.4 Gm. per cent, with albumin/globulin ratio of 2.9/2.5. Later examinations showed total protein 7.4 Gm. per cent, with albumin/globulin ratio of 3.1/4.3 and 3 plus cephalin flocculation; total protein 8.4 Gm. per cent, with albumin/globulin ratio 4.2/4.2 and plus-minus cephalin flocculation; total protein 8.0 Gm. per cent, with albumin/globulin ratio of 3.9/4.1 and plus-minus cephalin

flocculation and total protein 8.0 Gm. per cent, with albumin/globulin ratio 3.9/4.1 and plus-minus cephalin flocculation. A spontaneously precipitable protein appeared during this time. After a stormy course penicillin therapy resulted in recovery and the patient left against advice on the sixtieth hospital day. Because the blood culture of February 18, 1947, was positive, final diagnosis was septicemia caused by hemolytic streptococcus. Since only one positive blood culture was obtained, the staff was not satisfied with the diagnosis and chose to consider the case as possible polyarteritis nodosa. The patient returned for follow-up study several times and a small amount of spontaneously precipitable protein was found. He refused another muscle biopsy when last seen, about nine months ago.

In this case a spontaneously precipitable protein appeared with the elevation of the total protein and the reversal of the albumin/globulin ratio, even in the absence of strongly positive cephalin flocculation. Azotemia was also present.

CASE VI. J. S., a sixty-four year old white male, was admitted on March 9, 1948, because of pains in the legs and a burning sensation in the soles of his feet present for five weeks, causing such discomfort that he could not rest day or night. He had been treated in two other hospitals since 1941 for a duodenal ulcer, gallbladder disease and myocardial infarction. Extensive investigation in 1943 showed a duodenal ulcer with marked deformity of the duodenal bulb and crater of the posterior wall. In May, 1946 the duodenal ulcer perforated and surgical repair was performed. In July, 1947 and September, 1947 he was treated for bleeding ulcer. Blood pressures were 170/110, 190/110 and 170/100. Urinalyses varied from a trace of albumin to 3 plus albumin, with occasional casts, white blood cells and red blood cells. Some arteriovenous nicking and diminution in the caliber of the fundal arterioles were noted.

On admission to Lincoln Hospital, March 9, 1948, he looked acutely ill, with a temperature of 101.4°F. and a blood pressure of 160/90. Urinalysis was negative. Electrocardiogram showed evidence of coronary insufficiency. When a spontaneously precipitable protein appeared in the first blood specimen withdrawn

for analysis, the diagnosis of polyarteritis nodosa was suggested. Clinical findings of hypertension, low grade fever and bizarre complaints, with the symptoms of peripheral neuritis, completed the picture.

On March 15, 1948, total protein before refrigeration of the blood specimen was 5.8 Gm. per cent, with an albumin/globulin ratio of 2.9/2.9. After refrigeration and removal of the precipitate total protein was 5.5 Gm. per cent, with albumin/globulin ratio of 2.7/2.8. Cephalin flocculation was 4 plus. Blood urea nitrogen was 46 mg. per cent and non-protein nitrogen was 85 mg. per cent. No eosinophilia was noted. Biopsy from the right deltoid region on March 22, 1948, showed fresh lesions of polyarteritis nodosa confirming the earlier clinical diagnosis. Urinalysis showed 2 plus albumin, 2 erythrocytes, occasional leukocytes and many granular and hyaline casts per high power field. Cephalin flocculation tests were persistently 4 plus. Blood urea nitrogen remained above 40 mg. per cent, with non-protein nitrogens 84, 90, 92, 91, 116, 73, 78 and—pre-terminally—112 mg. per cent. Other total proteins were 5.4 Gm. per cent, with albumin/globulin ratio of 2.7/2.7 and 6.4 Gm. per cent, with albumin/globulin ratio of 2.9/3.5. The amount of spontaneously precipitable protein observable varied from a small sediment to a relatively heavy deposit, but it was always indisputably present. The patient died in a uremic state on the seventy-second hospital day, May 20, 1948. Permission for autopsy was refused.

It is noteworthy that in this case the putative diagnosis of polyarteritis nodosa was made shortly after admission to the hospital on the basis of the appearance of a spontaneously precipitable protein in a patient with bizarre complaints. This diagnosis was made before the characteristic clinical course was observed and before confirmatory biopsy was obtained in a patient who had been carefully studied during the course of many admissions to another hospital.

METHODS AND MATERIALS

Blood drawn in the morning before breakfast was allowed to clot at room temperature for several hours. The serum was

separated by centrifugation. All sera were stored overnight in the refrigerator at 4°C.

Electrophoretic studies on the precipitate were carried out in a double-section Tiselius microcell (2 ml. capacity) at a concentration of 0.5 per cent. The electrophoretic study was made at pH 11.7, using a glycine-sodium hydroxide Sørensen buffer. At this pH the precipitate was judged sufficiently soluble for electrophoretic analysis. As a control a known sample of gamma globulin was run to determine its mobility under the same given conditions as the precipitate. This micro run also served to demonstrate the practicality of using the Sørensen buffer for electrophoretic studies. Runs on the precipitate were of 162 minutes duration, an adequate time interval for separation and measurement of the fractions involved. Electrophoretic studies on the supernatant sera after removal of the precipitate were carried out in a double-section Tiselius cell (11 ml. capacity) using a pH 7.6 phosphate buffer (ionic strength 0.2). Electrophoretic studies without dialysis on fresh serum—before and after spontaneous precipitation—were likewise carried out.

Microchemical analyses of the precipitate were carried out as follows: The precipitate with its supernatant serum was centrifuged at 1,500 revolutions per minute at 2°C. The precipitate was washed with 5 ml. of water at 2°C. and recentrifuged. The same washing procedure was repeated and the precipitate was resuspended in water and lyophilized. Nitrogen determination was done colorimetrically by Nesslerization. Phosphorus was determined by the method of Fiske and SubbaRow.

OBSERVATIONS

The amount of precipitate found varied in all six patients, as well as in any one patient under different conditions. The following preliminary chemical and physical characteristics were common to all precipitates in all six patients: (1) Maximum precipitation occurred after twenty-four hours, with little or no precipitation there-



FIG. 1. Electrophoretic pattern (descending boundary) of the irreversible precipitate in Case vi.

after. (2) On warming the serum to room temperature the precipitate did not redissolve. (3) No precipitation or turbidity was induced on centrifugation of serum at room temperature. (4) The precipitate gave a positive xanthoprotein reaction with concentrated nitric acid. (5) The precipitate cleared on heating slowly in a water bath at about 70°C., and coagulated at about 80°C. (6) It was not soluble in distilled water or in 0.9 per cent sodium chloride. (7) On attempting solution in 0.01 sodium hydrochloric acid a cloudy solution—or, appropriately, a suspension—resulted from which no reprecipitation could be obtained on standing or on centrifugation. (8) A precipitate was noted on treating the suspension first described with 22.2 per cent sodium sulfate (Howe's method).

As a result of these preliminary examinations we were able to define the precipitate as a protein and specifically as a globulin.

Various technical and practical difficulties prevented quantitative and electrophoretic studies in our first five patients. In the sixth patient these studies were performed with the following results: (1) The dry weight of the precipitate was 0.08 Gm. per 100 ml. of serum. This value varied in the same patient in different stages of the disease. (2) The precipitate obtained by centrifugation of the serum in the cold followed by several water washings was increasingly soluble at increasing pH in the range studied (pH 7 to pH 12). It was judged sufficiently soluble at pH 11.7 for an electrophoretic run. (3) Results of the electrophoretic run on the precipitate (Fig. 1) showed it to be a non-homogeneous substance with a large slowly

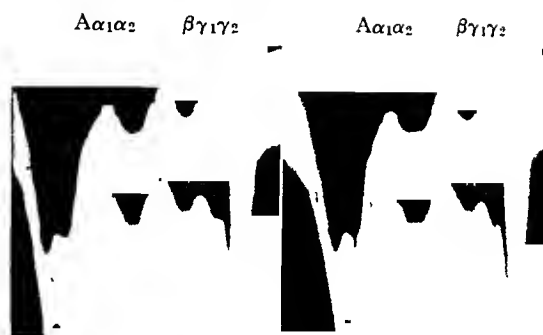


FIG. 2. Electrophoretic patterns (ascending boundaries) of fresh serum (A) before any precipitation and (B) after removal of precipitate in Case vi.

moving component and at least one fast moving component. The calculated mobility for the large component was 5.7×10^{-5} cm²/volt/second, and for the smaller one 7.5×10^{-5} cm²/volt/second. All calculations were based on the descending boundaries. (4) Microchemical analyses of the precipitate showed the nitrogen content to be 13.9 per cent and the phosphorus content to be 0.16 per cent. (5) Electrophoretic analysis of the supernatant serum after withdrawal of the precipitate for electrophoresis revealed the following distribution of components in percentage concentration:

Total protein....	6.4 Gm. %
Albumin.....	37% (normal, 57.5%)
Alpha globulin.....	10% (normal, 14.4%)
Beta globulin... ..	11% (normal, 16.5%)
Gamma globulin.....	42% (normal, 11.7%)

Electrophoretic analysis of fresh undialyzed serum before precipitation, and analysis performed after precipitation revealed the following distribution, utilizing the ascending limbs of both curves. (Fig. 2.)

	Albumin	Alpha ₁	Alpha ₂	Beta	Gamma ₁	Gamma ₂
Before precipitation, (% concentration).....	33.8	5.8	7.7	12.3	18.8	21.6
After precipitation, (% concentration).....	37.8	6.2	8.0	11.6	24.0	12.4

COMMENTS

The precipitate described herein differs from that noted by Stein and Wertheimer¹ who reported a precipitate which redissolved at room temperature. This did not occur in our patients. In a follow-up report Wertheimer and Stein² described a precipitate which they termed the "cold fraction," to indicate that protein portion of serum which precipitates when the serum stands for twenty-four hours at 7° to 11°C. In most instances reported by these workers the precipitate redissolved at room temperature. Our precipitate has the same characteristics as the "cold fraction" plus one additional feature—precipitation is irreversible on rewarming to room temperature. In this respect this fraction is also unlike those reported by Lerner and Greenberg,³ Atlas et al.,⁴ Holmberg and Grönwall⁵ and Shapiro and Wertheimer.⁶ In addition it is unlike the cold-susceptible proteins precipitated in multiple myeloma, as reported by Bing,⁷ Wintrobe and Buell⁸ and Von Bonsdorff et al.⁹ Lerner and Watson¹⁰ and Lerner et al.¹¹ later introduced the term "cryoglobulin" and gave various physical and chemical data showing that their protein was not unlike a gamma globulin. Analysis of electrophoretic patterns and of results of the various chemical and physical investigations described for our precipitate would seem to indicate that it probably comprises one or more of the group making up the gamma globulin fraction.

The gamma globulin fraction has been found to contain many of the known antibodies. A rise in gamma globulin has been noted in many infectious diseases.^{13,14} It is possible that the elevated gamma globulin found in our patients, all of whom were chronic cases, may be in the nature of a "reagin." In support of this postulate one

of the etiologic factors in polyarteritis nodosa has been thought to be allergic in nature.

In our series of six patients Cases I, II and VI were definitely proved to be polyarteritis nodosa. In Case III exitus followed rapidly after admission to the hospital, leaving insufficient time for an adequate study. In view of the suggestive clinical and laboratory data the possibility of polyarteritis nodosa definitely cannot be eliminated. In Case V the possibility of polyarteritis nodosa is also strong.

SUMMARY

Studies were made on the serum of a proved case of polyarteritis nodosa in which the appearance of a spontaneous precipitate at 4°C. had been noted. The observed spontaneously precipitable protein differed from previously reported "cold fractions" or "cryoglobulins" in not redissolving at room temperature. Electrophoretic studies indicated that it is one component of the group of gamma globulins.

The observed spontaneously precipitable protein also appeared in other cases—but not always—in which there was a reversal of the albumin/globulin ratio in the presence of a strongly positive cephalin flocculation reaction and of azotemia. The total serum protein was not actually elevated but it was usually increased from a relatively low value to a normal or slightly high normal with progress of the disease.

Since this same type of precipitate had been observed in two other proved cases of polyarteritis nodosa, the suggestion is offered that polyarteritis nodosa should be suspected when an irreversible spontaneous protein precipitate appears in the serum of a patient with a bizarre clinical picture.

Acknowledgments. Acknowledgments are made to Kenneth Taylor, M.D., Director of Medicine, Lincoln Hospital, for his invaluable aid and encouragement, making this work possible; Dan H. Moore, Ph.D., Columbia University College of Physicians and Surgeons, for his cooperation in electrophoretic studies and Samuel Alpert, M.D., Lincoln Hospital, for his cooperation in clinical and laboratory investigation of Case IV.

REFERENCES

1. STEIN, L. and WERTHEIMER, E. A new fraction of cold susceptible protein in blood of dogs infected with kala-azar. *Ann. Trop. Med.*, 36: 17, 1942.
2. WERTHEIMER, E. and STEIN, L. The cold susceptible globulin fraction of pathologic sera. *J. Lab. & Clin. Med.*, 29: 1082, 1944.
3. LERNER, A. B. and GREENBERG, G. R. A homomolecular serum protein with anomalous solubilities. *J. Biol. Chem.*, 62: 429, 1946.
4. ATLAS, D. H., CARDON, L., BUMATA, J. Note on use of Kagan falling drop proteinometer. *Am. J. Clin. Path.*, 13: 21, 1942.
5. HOLMBERG, C. G. and GRÖNWALL, A. A new crystalline serum globulin. *Ztschr. f. physiol. Chem.*, 273: 199, 1942.
6. SHAPIRO, B. and WERTHEIMER, E. Spontaneous crystallization of a protein from pathologic human serum. *Brit. J. Exper. Path.*, 27: 225, 1946.
7. BING, J. Further investigations on hyperglobulinemia. *Acta med. Scandinav.*, 103: 547, 1940.
8. WINTROBE, M. W. and BUELL, M. Hyperproteinemia associated with multiple myeloma. *Bull. Johns Hopkins Hosp.*, 52: 156, 1933.
9. VON BONSDORFF, B., GROTH, H. and PACKALEN, T. On the presence of a high molecular crystallizable protein in blood serum in myeloma. *Folia haemat.*, 59: 184, 1938.
10. LERNER, A. B. and WATSON, C. J. I. Studies of cryoglobulins. *Am. J. M. Sc.*, 214: 410, 1947.
11. LERNER, A. B., BARNUM, C. P. and WATSON, C. J. II. Studies of cryoglobulins. *Am. J. M. Sc.*, 214: 416, 1947.
12. BENDITT, E. P. and WALKER, S. A. Serum proteins in syphilis. *Am. J. Med.*, 4: 663, 1948.
13. GRAY, S. J. and BARRON, E. S. G. The electrophoretic analysis of the serum proteins in diseases of the liver. *J. Clin. Investigation*, 22: 191, 1943.
14. SEIBERT, F. B. and NELSON, J. W. Electrophoresis of serum proteins in tuberculosis and other chronic diseases. *Am. Rev. Tuberc.*, 47: 66, 1943.

Acute Diffuse Glomerulonephritis*

JAN BROD, M.D.

Prague, Czechoslovakia

A CENTURY separates us from Bright's classical description of the disease which bears his name; since then, many attempts at subclassification have been undertaken and several syndromes have been described, but the etiology and pathogenesis of the disease still pose many unsolved problems. Much of our present knowledge is based on clinical studies from the first World War when acute nephritis occurred in soldiers in epidemic proportions. In the laboratory, however, many recent discoveries have been made, both in the field of renal physiology and as a result of the experimental production of acute nephritis in animals. We are faced with a wealth of facts but correlation lags behind.

Anticipating a possible epidemic of "trench nephritis" in the recent war, preparations were made at the 103rd British General Hospital in the field for planned clinical research. Although no epidemic occurred, a number of patients were studied and these studies seem to throw new light on some of the problems involved.

MATERIAL AND METHODS OF STUDY

The present report deals with sixty-two patients with acute glomerulonephritis, one with lipoid nephrosis and three with "nephritis with nephrotic syndrome," making a total of sixty-six. They were observed between May, 1943, and June, 1945, nine in North Africa and the rest in Italy. Only fourteen were direct admissions, the remainder being transferred from forward medical units. The patients were all soldiers, fifty-six from the United Kingdom, six from enemy prison camps and four from elsewhere.

Routine history reporting included a thorough inquiry into the patient's condition of health

during the four weeks preceding the onset of acute nephritis. An ophthalmologist's opinion was obtained in the event of any suspected or obvious abnormality of the eyegrounds. A fluid-balance chart was maintained on all patients. The blood pressure, urinary deposit and erythrocyte sedimentation rate were checked about once a week, more frequently or daily when in a phase of rapid change. Hemoglobin (Sahli), hematocrit values, and serum proteins (copper sulfate method) were estimated occasionally.

The following tests were used for the assessment of renal functions: (1) Dilution. The patient, after emptying his bladder, drank 2 pints of water within one-half to three-quarters of an hour. Specimens of urine were then collected hourly over the next four hours. The test was considered satisfactory if the total volume of urine passed exceeded 900 cc. and if the specific gravity dropped to 1.002 or below. (2) Concentration. Fluid deprivation was carried out for thirty-six hours, ending at 6 A.M. Normal concentration was indicated by a rise in specific gravity to at least 1.028. (3) Blood urea. Values up to 40 mg. per cent were considered normal. (4) Urea clearance. (5) Endogenous creatinine clearance. As inulin, considered to be a non-threshold substance with a clearance equal to the glomerular filtration rate, was unobtainable in the field, endogenous creatinine clearances, which are thought to be sufficiently near this value to warrant conclusions, were estimated instead. The amount of creatinine in the specimens was measured by the method of Popper. Mandel and Mayer¹ using a photoelectric colorimeter. The usual test consisted of three-hourly readings over a period of twenty-four hours, the curve so constructed giving a clearer picture of events than a single reading over a short time.² Normal curves exhibit marked fluctuations, the rate of filtration varying between about 80 and 180 cc. per minute: the higher readings usually occur during the first

* From The First Medical Clinic, Charles University, Prague, Czechoslovakia, and The Department of Physiology, New York University College of Medicine, New York, N. Y.

part of the day, the lower ones at night. Tubular reabsorption of water was calculated by subtracting the known volume of urine from the estimated volume of glomerular filtrate in unit time and is expressed as a percentage of the filtrate. In normal subjects this percentage is

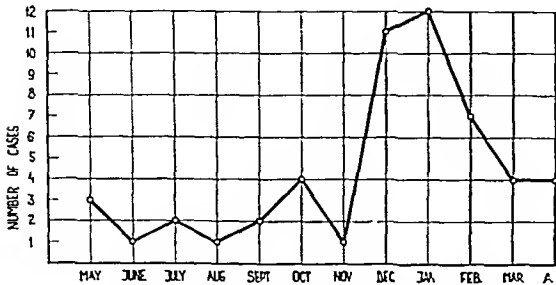


FIG. 1. Seasonal incidence of glomerulonephritis.

remarkably constant, being close to 99 per cent and rarely falling below 98.3 per cent unless the body is flooded with water. Reabsorption of 98 per cent of the filtrate is equivalent to a U/P ratio of 50, 99 per cent to a U/P ratio of 100 and 99.5 per cent to a U/P of 200.

HISTORY

Table I shows the incidence and nature of preceding infection in those of the present series. Some infection was found in fifty-eight of sixty-six cases, 87.8 per cent. The significant period was considered to be the thirty days preceding the onset of nephritic symptoms. The term "infection" includes simple sore throat, coryza, septic skin con-

ditions and diarrhea, the last often being due to Flexner or to allied bacilli prevalent in the Mediterranean area. In a control series of one hundred unselected hospital patients a past history of infection during the same interval was present in 46 per cent. Tonsillitis and infections of the upper respiratory tract were most frequent. This probably accounts for the high incidence of acute glomerulonephritis during the winter quarter (Fig. 1), thirty of fifty-two patients seen between May, 1944 and April, 1945 presenting themselves between December and March.

The interval between the beginning of the infection and the first manifestations of acute glomerulonephritis averaged 16.5 days. The figures represent the upper limit as the interval has been calculated from the first day of the preceding infection. Moreover, there is probably a time-lag between the first clinical manifestations of nephritis and the onset of the disease. One patient (Case 47) had an extensive vascular nevus involving the whole of the right upper limb and shoulder girdle. Sore throat occurred on January 1, 1945, and on the 14th he complained of lassitude and slight breathlessness on exertion. Eight days later the part of the body affected by the nevus became edematous, but edema did not become generalized until seven days later, i.e.,

TABLE I
INCIDENCE AND NATURE OF PRECEDING INFECTION IN ACUTE GLOMERULONEPHRITIS

Preceding Infection	No of Patients	Per cent	Longest Interval	Shortest Interval	Average Interval
Tonsillitis	23	34.8	30 days	0 days	15.6 days
Coryza	16	24.3	30 days	2 days	18.3 days
Diarrhea	10	15.1	30 days	1 day	16.0 days
Septic skin	5	7.6	30 days	5 days	16.3 days
Alveolar pyorrhea	1		Present for 3 months		
Pansinusitis	1		Present for 12 years, operation 7 days previously		
					7 days
Bronchopneumonia	1				5 days
Gonorrhea	1				2 days
No history of infection	8				
Total No. of patients	66	87.8	30 days	0 days	16.5 days
History of infection	58				

fifteen days after the first symptoms and twenty-nine days after the onset of tonsillitis. It is clear that the tendency toward edema was present one week before it became obvious in those parts of the body where the capillaries were not, *a priori*, abnormal.

An interesting feature was the association of acute glomerulonephritis with typical rheumatic fever in six instances. The latter preceded the first manifestations of nephritis by fourteen to seventeen days in four patients, followed them by thirteen days in the fifth and commenced simultaneously with nephritis in the sixth. Two of these patients had Schoenlein-Henoch's rheumatic purpura and another developed urticaria four days before onset of the first symptoms of acute glomerulonephritis.

CLINICAL FEATURES

Tables II and III summarize the symptoms and signs encountered, with their relative frequency, time of appearance and duration.

General Constitutional Symptoms. These symptoms were present to some extent in the majority of subjects. Headache occurred in about one-half, backache in about one-

third and lassitude in one-fifth; these symptoms could not be traced to any specific phase of the morbid picture. Nausea and vomiting, which occurred at the onset in six patients, were always associated with an increased blood urea concentration although the reverse was not true. Vomiting

TABLE II
PRESENTING SYMPTOMS OF ACUTE GLOMERULONEPHRITIS
IN ORDER OF FREQUENCY

Symptom	Incidence	
	No.	Per cent
Edema.....	49	74.2
Dyspnea.....	42	63.6
Headache.....	32	48.0
Macroscopic hematuria.....	26	39.3
Backache.....	22	32.0
Oliguria (observed by the patients)...	13	19.6
Lassitude.....	13	19.6
Exaggerated thirst.....	11	16.0
Fever.....	9	13.6
Frequency.....	7	10.0
Vomiting.....	6	9.0
Dysuria.....	3	4.5
Epistaxis.....	2	3.0

TABLE III
SIGNS OF ACUTE GLOMERULONEPHRITIS

Sign	Incidence		Present at Onset	Appeared Subsequent to Onset	Subsided	In Instances in Which It Subsided		
	No. of Instances	Per cent				Shortest Duration (days)	Longest Duration (days)	Average (days)
Oliguria.....	47	71.2	47	..	45	7	54	21.5
Anuria.....	2	3.0	1	1	2	1	2	
Albuminuria.....	66	100.0	65	1	8	10	145	64.0
Hematuria.....	64	96.9	64	..	20	14	167	72.4
Granular casts.....	58	87.8	47	5	25	5	139	51.7
Edema.....	60	90.0	55	5	52	2	122	34.8
Pleural effusion.....	3	5.0	3	..	3			
Pericardial effusion.....	1	1	..	1			
Ascites.....	1	1	..	1			
Hypertension.....	57	86.3	51	6	55	7	140	37.6
Dyspnea.....	43	65.1	42	1	43	7	90	20.3
Pulmonary edema.....	8	12.1	5	3				
Hypertensive encephalopathy.....	3	4.5	..	3				
Retinal changes.....	7	10.0	5			
Raised non-protein nitrogen.....	23	71.9	21	2	23	?	70	

also heralded all attacks of hypertensive encephalopathy.

Oliguria. Oliguria was noted at the onset in three-quarters of the patients. Anuria lasting one to two days occurred in only two instances.

Urinary Findings. Albuminuria, hematuria and casts were usually persistent and in the majority of patients were still present when they were evacuated. Granular casts and renal epithelial cells were present in the urine at the onset in over fifty patients. Dysuria and frequency occurred in twelve patients. All of them had marked albuminuria and macroscopic hematuria and in addition four had a moderate number of pus cells.

Edema. Edema had the usual features of a "nephritic" hydrops; it was accompanied three times by clinically identifiable pleural effusion, once by pericardial effusion and once by ascites. On the average it lasted 34.8 days and subsided in all but the three patients with "nephritis with nephrotic syndrome." It was frequently the first manifestation of disease, but in eleven patients it followed other symptoms by four to twenty-one days.

Hypertension. Hypertension was present in fifty-seven patients and was maintained for an average of 37.6 days; it was usually mild or moderate but reached 200 mm. Hg systolic or above in nine patients. The highest reading was 215/130 mm. Hg. It was accompanied by some degree of breathlessness in forty patients; dyspnea occurred independently only twice and was associated with gross edema. While no regular relationship could be established between breathlessness and edema, there was no doubt about the relationship between breathlessness and hypertension. In most instances it occurred only on exertion and disappeared shortly after the patient had been put to bed, but five patients developed acute pulmonary edema and three had numerous basal rales. Excluding two patients in whom there was reason to suspect previous hypertension, no signs of left ventricular hypertrophy were found. Elec-

trocardiograms were taken occasionally and were within normal limits.

Hypertensive Encephalopathy. Hypertensive encephalopathy complicated three instances of the disease and occurred on the seventh, twelfth and fourteenth day. It was heralded by severe headache, vomiting and a sharp rise in blood pressure. Two of the patients had one attack only, the third had three attacks. One was treated with venesection, the other two with sedatives and all recovered promptly.

Retinal Changes. Retinal changes were observed in seven patients. All had considerable hypertension, ranging from 175/100 to 205/130 mm. Hg. Two had retinal hemorrhages only, three had papilledema and two presented a typical picture of "hypertensive neuroretinopathy." The fundi in those patients with only hemorrhages or papilledema returned to normal while the patient was still under observation, whereas "hypertensive neuroretinopathy" persisted and was still present in the two patients so afflicted when they were evacuated, several months after the acute stage had subsided and long after the blood pressure had returned to normal. In all other respects both patients seemed to have typical acute glomerulonephritis; there was no evidence of a previous attack or of previous hypertension; routine urinary examination was said to have been performed on enlistment with negative results.

RENAL FUNCTION TESTS

Blood Non-protein Nitrogen. The blood non-protein nitrogen was elevated at the onset in twenty-three of the thirty-two patients in whom it was determined; in about one-half of them it quickly returned to normal but remained elevated after one month in eight patients and after sixty days in four.

Dilution Test. This test usually demonstrated fluid retention in the initial stage. Although slight diuresis, with a fall of specific gravity to 1.002 or below, was usually detected during the first hour or two, this soon stopped and the total output

was below normal. This behavior suggests that the failure to dilute at this stage was not due to the kidneys, which evidently responded properly to the stimulus, but to changes in fluid balance. In the later stages similar behavior was encountered in eight patients, pointing again to fluid imbalance.

2. All the patients recorded here were in satisfactory fluid balance. In the group with renal epithelial cells or granular casts in the urinary deposit, which are indicative of a severe degenerative process in the tubular epithelium,³ satisfactory concentration was achieved only four times in seventy in-

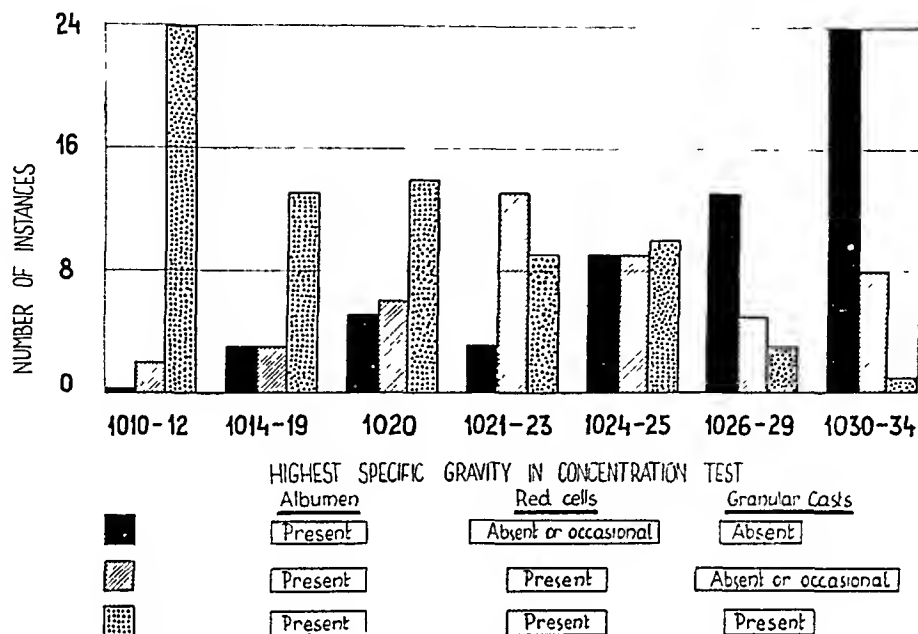


FIG. 2. Relationship of concentrating power and urinary findings.

No response to fluid ingestion occurred in five patients and the specific gravity of the urine remained fixed. In these patients there was additional evidence indicating serious renal damage.

Only fifteen patients in the whole series showed an impaired water dilution test, which may be related to the relatively small proportion of direct admissions.

Concentration Test. On the other hand, the concentration test revealed impaired function in forty-three patients, even as early as the third day. Improvement in this respect was poor and slow, the figure remaining virtually unchanged until final disposal in twenty-four patients and returning to normal in only nine; in ten there was some improvement over the period of observation and in six there was deterioration. All five patients who were unable to dilute had very restricted concentrating power, in four amounting to isosthenuria. That loss of concentrating power is directly related to tubular damage can be seen from Figure

stances while in the group with only albumin and/or erythrocytes in the urine, both of which are thought to be of glomerular origin, normal concentrating power was recorded in twenty-seven of fifty-six instances.

As both dilution and concentration are functions of the renal tubules, the greater impairment of concentrating power needs explanation for thirty-eight patients with impaired or abolished concentrating power diluted normally. The discrepancy is probably due to dissociation of these two tubular functions, concentrating power being impaired in renal disease earlier than diluting power. Evidence is accumulating that the concentrating power depends upon the functional integrity of the distal tubule, the water re-absorption of the proximal tubule proceeding isosmotically,⁴ a process for which Smith⁵ suggested the name of "obligatory reabsorption." This process normally accounts for the conservation to the body of about 87 per cent of the water

filtered through the glomeruli. It is, however, in the distal tubule that by a process of "facultative reabsorption" the remaining 13 per cent of the filtrate undergoes an osmotic change, water reabsorption proceeding against the osmotic gradient created

were submitted to a second concentration test, during which 1 cc. of pituitrin was injected subcutaneously every two hours. Sensitivity to the antidiuretic action of pituitrin was previously established by observing its effects on the dilution test. In

TABLE IV
EFFECT OF PITUITRIN ON IMPAIRED POWER OF CONCENTRATION

Dilution Test					Concentration Test				
Case No.	Total Volume of Urine (cc. excreted in 4 Hr.)		Lowest Specific Gravity		Total Volume of Urine (cc. in 24 Hr.)		Highest Specific Gravity		Maximal Reabsorption in Per cent of Glomerular Filtrate
	Ordinary Test	With Pituitrin	Ordinary Test	With Pituitrin	Ordinary Test	With Pituitrin	Ordinary Test	With Pituitrin	
33	755	...	1.000	1840	1390	1.024	1.019	99.5
32	1000	210	1.000	1.020	890	530	1.018	1.020	99.6
28	850	230	1.000	1.016	1060	860	1.020	1.020	99.5
51	800	400	1.000	1.010	1010	980	1.020	1.016	99.4
47	640	390	1.000	1.015	1345	1125	1.014	1.016	99.0
49	1025	220	1.000	560	790	1.024	1.017	99.5
45	915	315	1.000	1035	540	1.020	1.022	99.5
43	1000	250	1.000	1.010	1600	1050	1.024	1.018	99.4
52	1280	240	1.000	940	900	1.016	1.015	99.7
34	1030	...	1.000	1295	1310	1.020	1.015	99.3
37	1035	285	1.000	1.016	1090	1050	1.018	1.022	99.3
31	1000	...	1.000	1240	1065	1.015	1.015	99.0
39	1750	...	1.000	850	1090	1.022	1.024	99.3
56	1525	...	1.002	700	700	1.020	1.020	99.5

by urea, salt and other unreabsorbed substances. It is this distal tubular segment which seems to respond to the requirements for water, conserving up to 99.8 per cent of the filtrate in cases of dehydration and rejecting up to some 13 cc. of every 100 cc. of filtrate under conditions of maximum hydration. This function is to a great extent, but not entirely,⁶ under the influence of the antidiuretic hormone (ADH) of the posterior lobe of the pituitary. The poor results of the concentration test consequently could be due either to failure of the pituitary to respond to conditions of dehydration or to a lack of sensitivity or inability of the distal tubular cells to respond to the stimulus of an antidiuretic hormone.

To examine the matter further fifteen patients with poor concentrating power

all instances tested pituitrin could prevent water diuresis. (Table iv.) The maximum concentrating power, however, remained unaffected and in a few instances was slightly less with pituitrin than without its use. The total output of urine in the concentration test diminished further under the influence of pituitrin only in one-half of the patients, indicating that in the remainder the tubules may have been subjected to the maximum effect of endogenous ADH during the first concentration test without pituitrin.

From these observations it may be inferred that the inability to concentrate in acute nephritis is not due to some disturbance in the secretion of the ADH nor is the distal tubule insensitive to the antidiuretic action of this hormone. Further

evidence that there is no failure to reabsorb water in acute nephritis will be presented later. The loss of concentrating power therefore points to impairment of the osmotic function of the distal tubule alone, which suffers long before there is any reduction in the capacity to dilute.

With organic destruction of glomeruli, as seen in chronic nephritis, the filtration rate falls below the normal level and to maintain as normal a function as possible all the available glomeruli have to function continuously at a maximum rate;⁸ variations are minimal and the curve is rigid. (Fig. 3c.)

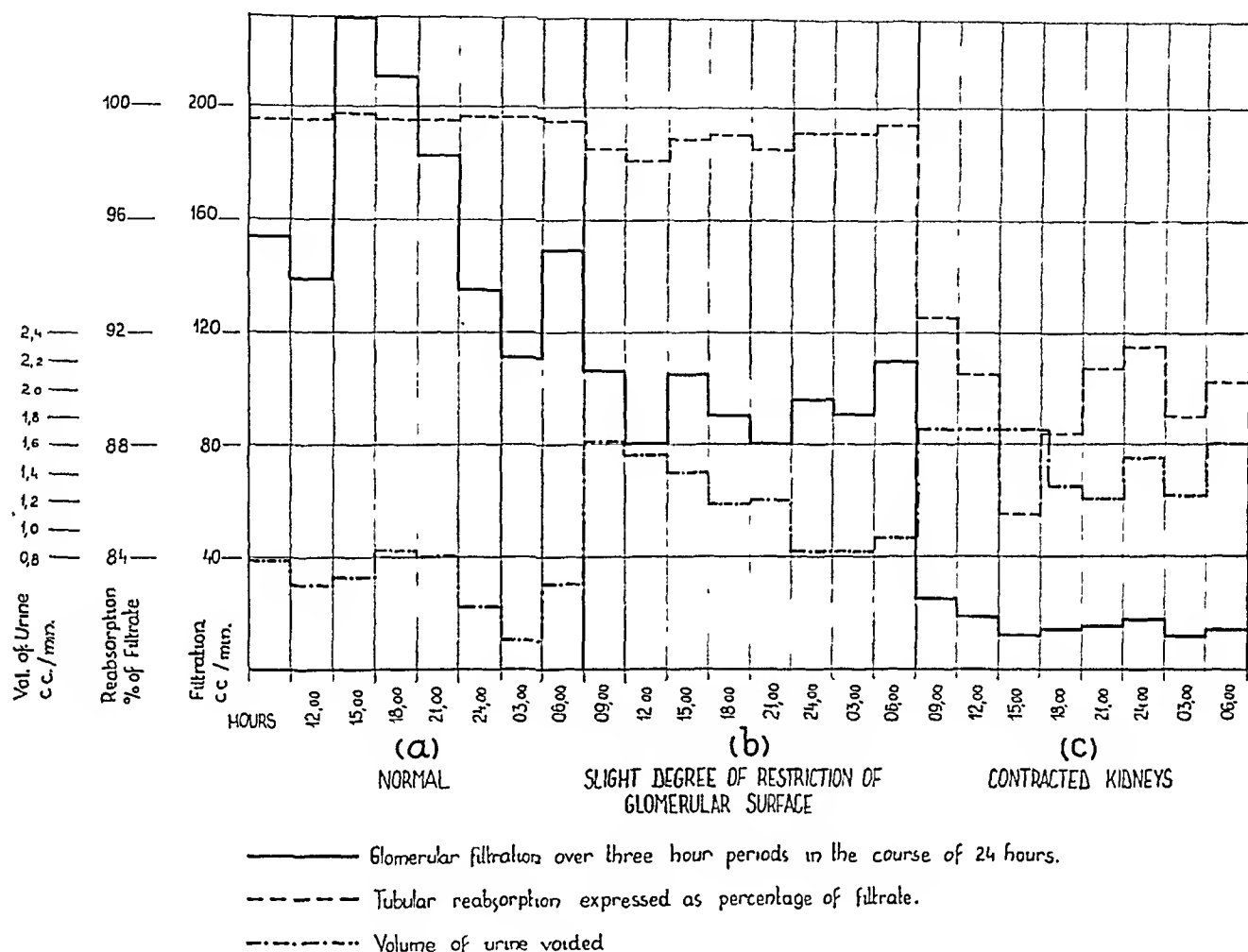


FIG. 3. Curves of glomerular filtration, tubular reabsorption of water and diuresis over a twenty-four-hour period; *a*, normal kidneys; *b*, slight degree of restriction of glomerular surface; *c*, contracted kidneys.

Endogenous Creatinine Clearance. Creatinine clearance was measured over successive three-hour periods for twenty-four hours in seventy-nine instances and on forty-seven patients. Smith⁷ has deduced from observations of glucose Tm on normal human kidneys that there is probably no reserve of active glomeruli. The extent of glomerular activity depends, however, on hemodynamic changes in the kidney and varies according to the body requirements. Consequently, curves of glomerular activity constructed over a twenty-four-hour period will show marked fluctuations. (Fig. 3A.)

This may also happen in acute glomerulonephritis when sufficient numbers of glomeruli are out of action. In these patients significant elevation of blood urea above 40 mg. per cent did not occur until glomerular filtration was fixed below 50 cc./min. In less severe cases, as judged by other tests, the level of glomerular filtration was somewhere near the lower limit of normal and in milder cases fluctuation appeared (Fig. 3B), suggesting a variability in glomerular activity. In our series filtration was invariably normal (fourteen instances) when there was albuminuria alone

or with slight hematuria but no granular casts, and when the concentration test was normal. When granular casts were associated with similar findings, filtration was normal in eight instances and relatively fixed in the neighborhood of the lower limit of the normal in five. When impaired concentration was present, however, filtration was normal in twelve instances, relatively fixed near the lower limit of normal in twenty-one, below this limit but showing fair fluctuation in fifteen and low and rigid in four; in other words, it was abnormal in forty of fifty-two instances. It is to be noted, however, that filtration was normal in twelve instances (ten patients) in which concentration was impaired, whereas concentration was never normal when filtration was impaired although it was normal in five instances in which filtration was relatively fixed but still within the normal range. This indicates again that the concentrating power is a very sensitive function and probably the first indicator of a tubular disturbance which, as Earle, Taggart and Shannon⁹ have demonstrated, generally accompanies a reduction of filtration rate.

In following the course of sixteen patients with impaired filtration when first measured, serial filtration curves returned to normal within one to four months in eight instances, improved in two others and remained more or less static in the remainder. Of those whom returned to normal, five still had granular casts and two also showed impaired concentration. When filtration curves remained fixed although not necessarily below the lower limit of the normal, granular casts were always found, and impaired concentration occurred in six of eight patients. Nor was it possible to predict the course of filtration by the nature of the filtration curve; thus two patients with initially rigid and low values returned rapidly to normal, and the tendency toward recovery was the same whether early filtration levels were low but retained fluctuation or whether they were within normal limits but relatively fixed.

Total Tubular Reabsorption. Tubular re-

absorption of water was calculated from the filtration rate and urine flow in all instances. Its reduction and increase in variability is one of the most constant features in chronic nephritis in which glomeruli have lost all adaptability and the only remaining regulating mechanism is tubular. (Fig. 3c.) Chasis and Smith¹⁰ produced evidence that this reduction of reabsorption in nephritis is attributable in part to reduction in the "obligatory" reabsorptive process, perhaps through failure to reabsorb electrolytes proximally, thus producing osmotic diuresis. In acute glomerulonephritis, however, the total tubular reabsorption of water is usually normal and was found so in 80 per cent of those in the present series. Even when abnormal, reduction was usually slight and rarely fell below 96 per cent of the filtrate ($U/P = 25$). We have pointed out the failure to concentrate is not due to an inability of the distal tubule to respond to an ADH stimulus. This is further borne out by our data on reabsorption of water in fourteen instances of acute glomerulonephritis with impaired concentrating power. (Table iv.) In all cases tubular reabsorption could reach the normal maximum level (99 to 99.7 per cent). Consequently, in none of them was there a failure of "facultative reabsorption" of water, but this process lost its efficiency due to the inability of distal tubular cells to produce osmotic work.

Urea Clearance. Urea clearance provided little additional information to that given by the filtration curves. In few instances was it found below 60 per cent of the normal average and never below 40 per cent. Goldring and Chasis¹¹ have shown that on a constant protein diet the blood urea varies inversely with the urea clearance, as it should in theory. Conditions in a military hospital, however, made it impossible to eliminate all the possible factors which tend to obscure this relationship.

OTHER TESTS

As seen in Figure 4 the erythrocyte sedimentation rate (E.S.R.) was almost in-

variably raised in the initial phase, often considerably. It fell to lower levels in harmony with clinical improvement but reached normal only when the patient was cured or left with but minor urinary changes. Some of the curves show a clear division into two phases: the first sloping steeply downward in association with relatively rapid subsidence of hypertension and edema, the second rather horizontal and parallel with the much slower improvement in concentration and urinary findings. The degree of acceleration of the E.S.R. in this latter part of the graph was proportional to the severity of the renal lesion, being highest when renal function was grossly impaired and abnormal ingredients in the urinary deposit were conspicuous, and lowest when renal function was normal and the urine showed little but albuminuria. (Fig. 5.)

The blood picture was rarely altered, hemoglobin being below 80 per cent on five occasions and below 70 per cent once. Slight polymorphonuclear leukocytosis was detected occasionally at the onset. Observations on serum proteins and hemocrit values were too few to warrant any conclusions.

PARTIAL SYNDROMES

While the great majority of cases were characterized by transient hypertension and edema, by impaired glomerular filtration with or without retention of non-protein nitrogen, by hematuria and albuminuria and by poor concentration and granular cases in the urine, i.e., by all the well known features of the disease, a limited number of patients revealed or developed only part of the picture. As it is thought that these instances throw light on the pathogenesis of acute glomerulonephritis they will be described in more detail:

Hypertension and Edema without Nephritis:

CASE 18. The patient was a man aged twenty-eight. He had been treated in this hospital for hiccup thought to be due to basal pleurisy in April, 1944. On June 10, 1944, he developed breathlessness on exertion. On the

15th he noticed a "blotchy" rash on both legs which subsided after forty-eight hours. On the 17th painless swelling appeared in both legs and three days later his face became puffy and he was admitted to the hospital.

On examination his temperature was 99.2°F.

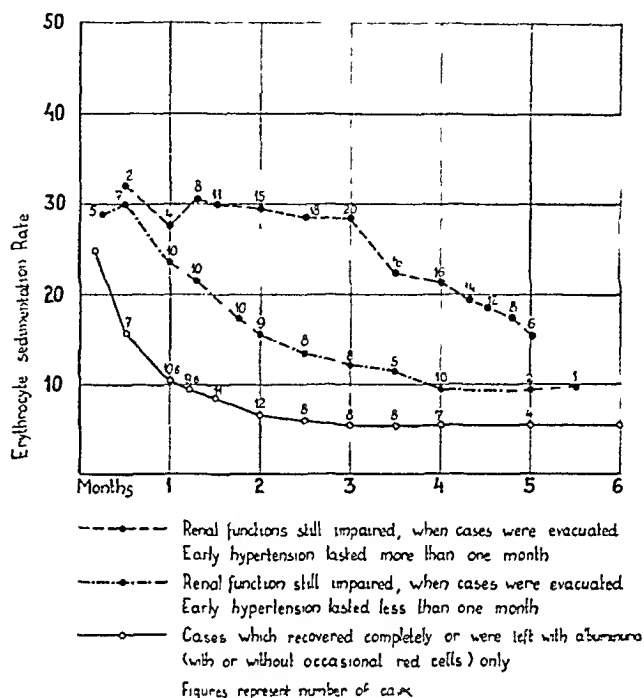


FIG. 4. Progress of changes of the erythrocyte sedimentation rate in the course of the disease, grouped according to the duration of the acute stage and the final outcome.

His face, sacrum and both legs were edematous and his blood pressure was 170/95. Venous pressure was normal and no abnormality was detected in the heart, lungs, central nervous system or ocular fundi. Contrary to expectation, examination of the urine disclosed no abnormality; there was no albumin and no abnormal elements were found in the urinary deposit. The E.S.R. was 14 mm. (Wintrobe), white blood cells numbered 5,350 per cm. (polymorphonuclears, 47 per cent, lymphocytes, 52 per cent; monocytes, 1 per cent) and blood urea, 28 mg. per cent.

He had marked oliguria, passing on June 22nd only 100 cc. of urine in twenty-four hours. He was treated by a forty-eight-hour period of complete food and fluid starvation (June 21st and 22nd), followed by a period of restricted fluid intake and low protein diet. Hypertension persisted until June 23rd; on June 24th it fell to 145/85 and on the 25th to 135/90 and eventually settled around 105/70. Parallel with its fall, edema started to disappear and diuresis increased correspondingly, the volume of urine exceeding the fluid intake by 1,100 cc. on

of August, but albuminuria and microscopic hematuria with granular and epithelial casts persisted throughout the four-months period of observation. At the time of the patient's evacuation to the United Kingdom toward the end of December, 1944, renal functions were still grossly impaired; the highest specific gravity of urine in the concentration test was 1.020, the lowest in the dilution test, 1.005; the blood urea was 50 mg. per cent and the urea clearance 58 and 62 per cent of the normal standard, with a rigid low curve of glomerular filtration around 50 cc. in one minute as measured by endogenous creatinine clearance; tubular reabsorption was still diminished, swinging between 95.8 and 98.6 per cent of the filtrate. Apart from poor concentration of dye, intravenous pyelography did not show anything abnormal and urine cultures were repeatedly sterile. Despite evidence of considerable renal damage, the blood pressure remained at 110/70 throughout and edema was never detected.

Case 37, admitted in January, 1945, was similar to Case 14. The picture was that of glomerulonephritis following febrile coryza, with urinary findings the same as in the previous patient. The highest specific gravity in the concentration test was 1.015 and there was marked oliguria; despite these findings there was neither edema nor hypertension. At this stage glomerular filtration was below normal and almost rigid, fluctuating between 55 and 85 cc./min.; tubular reabsorption was also lowered (96.3 to 98.5 per cent). The E.S.R. was 31 mm. per hour. After remaining in this condition for about two months the patient began improving slowly; the E.S.R. settled to normal levels in April, 1945, and at the time of his evacuation at the beginning of June, 1945, four months after the onset of his illness, he was left only with slight albuminuria and a few red cells and epithelial cells in the deposit; there was concentration to 1.028 and dilution was perfect; the filtration curve and tubular reabsorption became normal.

These two patients presented a picture of acute renal disease with all the characteristics of acute glomerulonephritis but in whom hypertension and edema were absent throughout in spite of severely impaired renal function and marked oliguria for at least seven days in both instances. Case 9 forms a link for it was similar to the last two

except that in the fourth week of illness fleeting edema was detected in both legs.

The details of two other cases are also worthy of note:

CASE 42. The patient, a man aged thirty-two, had several boils on his neck since March, 1945, and at the beginning of April developed hidradenitis axillaris. He became febrile on April 13th, with associated backache, and the next day he noticed that his urine was blood-stained and he complained of slight dysuria. On that day he was admitted to the hospital. The temperature was 101°F. Apart from the skin condition, physical examination revealed nothing abnormal; there was no edema and the blood pressure was 115/70. The urine contained albumin, large numbers of red cells, a few hyaline casts and renal epithelial cells. Urine culture was repeatedly sterile. White blood cells during the febrile stage numbered 6,900, 59 per cent being polymorphonuclears. After a few days the temperature settled and macroscopic hematuria subsided, but albuminuria with red blood cells, hyaline casts and scanty granular and epithelial casts in the deposits became a permanent finding and persisted at the time of his evacuation to the United Kingdom four months later. By then the boils had been healed for six weeks. Oliguria was absent throughout, the filtration curve was always normal, and only on one occasion, two weeks after the onset, was concentration power reduced, and then but slightly, the highest specific gravity reached being 1.025; four weeks later even this abnormality disappeared.

Case 39 was similar, except that no preceding infection could be traced. This patient was also febrile at the onset, had red blood cells and granular casts in the deposit, but no oliguria, no hypertension and no edema. The only functional abnormality was inability to concentrate above 1.024 during the second month of illness. At the time of his evacuation, five months after the onset, he still had marked albuminuria with microscopic hematuria and occasional renal epithelial cells in the deposit.

It is difficult to deny that these were instances of acute nephritis, especially as repeated urine cultures, blood counts and intravenous pyelograms were normal. All were soldiers who had had their urine examined on joining the Army and whose

physical condition had been repeatedly checked in the past.

It is possible to draw certain conclusions from these studies: First, it seems certain that hypertension, edema and oliguria can develop without evidence of a renal lesion. Second, a renal lesion having all the characteristic features of acute glomerulonephritis and accompanied by marked oliguria can develop without edema or hypertension. It follows that these two syndromes, although usually simultaneous, may exist independently of each other.

Nephrosis: Three patients will be described who were dominated by persistent edema and heavy albuminuria; the first two would ordinarily be regarded as examples of nephritis with nephrotic syndrome, the last as "pure nephrosis."

CASE 12. The patient, a Ceylonese aged twenty-six, fell ill September 10, 1944, with general malaise, fever and marked painless swelling of both legs, sacrum and face. He was admitted to the hospital on the same day. Apart from edema, investigation revealed nothing abnormal. The blood pressure was 100/65 and remained about the same throughout the period of observation. The urine was loaded with albumin and the deposit contained scanty red blood cells, hyaline casts and fairly numerous leukocytes and renal epithelial cells. Concentration was up to 1.026. The blood urea was not estimated at the onset but later was repeatedly about 30 mg. per cent. The initial edema tended to subside within the first four weeks but recurred in the sixth week and from then on remained stationary with minor variations throughout the three-months period of observation. The urine remained loaded with albumin and the deposit persistently showed about 5 red blood cells per high power field, hyaline and granular casts and renal epithelial cells. In spite of edema the dilution test was satisfactory on several occasions; concentration, however, deteriorated progressively, and shortly before evacuation the specific gravity of the urine could not be made to exceed 1.016. Total blood proteins were estimated at 4.8 Gm. per cent; the E.S.R. varied between 17 and 28 mm. in an hour.

CASE 58. The patient, a man aged twenty-nine, had slight puffiness of the face for four

months before developing marked generalized edema associated with severe albuminuria; only a few red blood cells and occasional epithelial casts were found in the deposit. During the first three weeks of generalized edema the blood pressure was elevated, the highest reading being 170/105. Edema and urinary changes persisted for at least four months when the patient was evacuated. Plasma proteins measured 4.5 Gm. per cent, the blood cholesterol 280 mg. per cent. The concentration was 1.032 and, although the dilution was 1.002, he excreted only 605 cc. in four hours. The blood urea was 26 mg. per cent. Glomerular filtration was rather rigid but within normal limits, oscillating about 100 cc./min. Tubular reabsorption was high, 99.5 to 99.7 per cent of the filtrate.

CASE 4. The patient had typical lipid nephrosis with marked albuminuria and extensive edema lasting for five months, with perfect renal functions and no hypertension. The urinary deposit contained hyaline casts but no red cells or other abnormal ingredients.

These patients form an interesting intermediate between diffuse glomerulonephritis and what is referred to as pure nephrosis. All had massive edema, heavy albuminuria and reduced plasma proteins. Case 12 showed impaired renal function and nephritic elements in the urinary deposit but no hypertension; Case 58 showed no impairment of renal function, minimal nephritic elements in the urinary deposit, but had transient hypertension; Case 4 showed normal renal function, had no nephritic elements in the urinary deposit and no hypertension. There can be no doubt that Cases 12 and 58 had acute glomerulonephritis. Had transient hypertension occurred in Case 12 instead of Case 58, the only difference between Cases 58 and 4 would have been the occurrence of a few red cells and occasional epithelial cells in the urinary deposit of the former. If the patient mentioned earlier with hypertension and edema only and no evidence of a renal lesion be rightly regarded as having the syndrome called acute glomerulonephritis, and considering the details of the patients presented illustrating all possible combinations of the various facets of this syndrome there seems

no valid reason to exclude Case 4. In other words, the evidence suggests that nephrosis is properly regarded as representing one aspect of the syndrome called glomerulonephritis.

COURSE

Hypertension subsided relatively quickly, usually within one to two months, in all but two patients in whom the rigidity and tortuosity of the brachial arteries associated with left ventricular dilatation and hypertrophy proclaimed previous essential or chronic nephritic hypertension. In one of these patients all evidence of nephritis disappeared while under observation; in the other considerable improvement had occurred in this respect when the patient was evacuated. The development of chronic nephritic hypertension was observed in only one patient, Case 33. In this patient the hypertension of the acute phase subsided in the usual time; there was an interval of three weeks during which the blood pressure was normal and the persistent hypertension developed while other features indicated established chronic nephritis.

Edema also subsided relatively quickly, usually within the same time as the hypertension, in all but four patients who presented the nephrotic syndrome; in three of them no gap between the early and chronic persistent phase was demonstrable.

In contrast to the behavior of hypertension and edema, impaired filtration, albuminuria, reduced power of concentration and granular casts in the urine were remarkably persistent. Thus, of fifty-three patients with primary acute cases commencing with hypertension, edema, impaired renal function and abnormal urinary constituents, only two remained in that category at the end of the second month; two remained edematous but not hypertensive; nine remained hypertensive but not edematous; four were cured; nine had abnormal urinary constituents only; the remaining twenty-seven had impaired renal function and abnormal urinary constituents but neither hypertension nor edema and

twenty-five were virtually unchanged at the end of four months. This dissociation between the course of hypertension and edema on the one hand and that of altered renal function on the other is well illustrated in Figure 6.

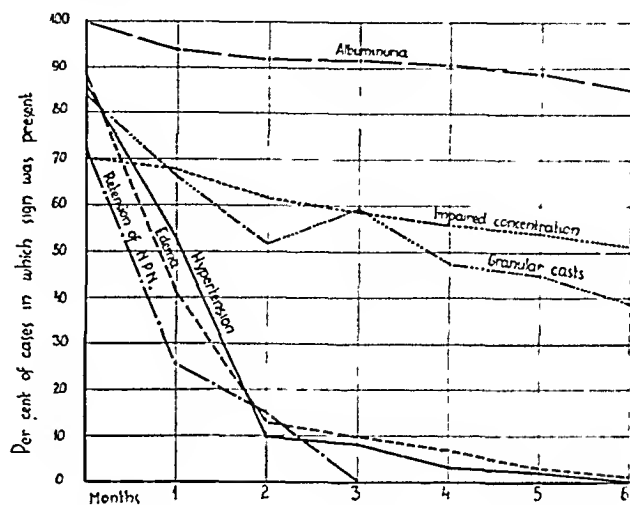


FIG. 6. Progress of the chief signs of the disease.

While the facts suggest that hypertension and edema are independent of the renal lesion, there is more evidence indicating that they are also independent of one another. Thus in Case 59 there was hyper-

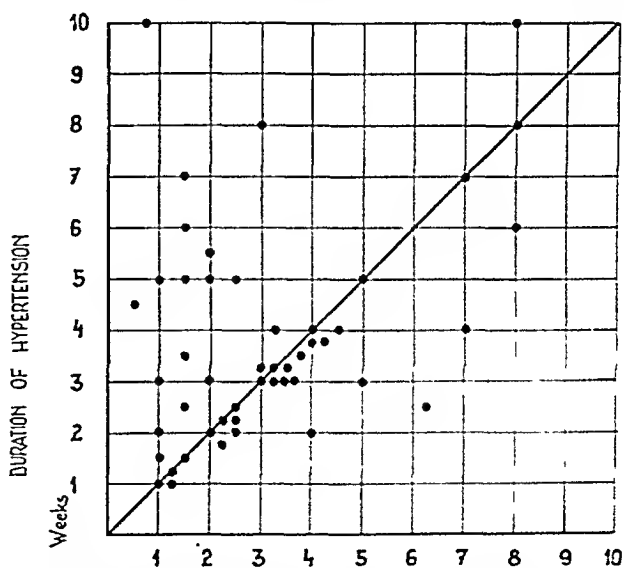


FIG. 7. Time relationship between duration of edema and hypertension.

tension but no edema; in Cases 12, 26, 58 and 60 there was edema but no hypertension; although in thirty-one instances both manifestations were closely associated, hypertension outlasted edema by one to nine weeks in fourteen instances and edema

outlasted hypertension by two to three and one-half weeks in five instances. (Fig. 7.)

Oliguria, of course, is necessarily intimately linked with edema. Yet even here partial dissociation can be demonstrated. (Fig. 8.) In addition to those patients (Cases

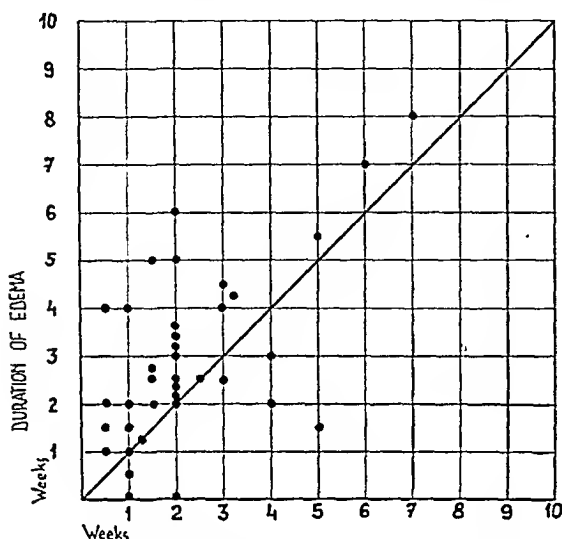


FIG. 8. Time relationship between oliguria and edema.

14 and 37) in whom marked oliguria for seven days failed to result in detectable edema, there were other instances in which edema subsided while oliguria persisted and yet others in whom edema persisted long after the establishment of good fluid balance.

Further scrutiny of Figure 6 reveals that nitrogen retention runs parallel with hypertension and edema and indeed was found after the first month only in those patients in whom hypertension was still present.

It has already been noted that the first phase of the E.S.R. graph also appears to be associated with these acute events while the second and more horizontal part of the curve reflects relatively persistent renal damage.

PROGNOSIS

There are few diseases in which reports on prognosis have differed so widely. On the whole the recovery rate is inversely proportional to age and perhaps to the accuracy and number of tests employed in its assessment. Figures for several series of cases occurring among soldiers in the first

world war were more constant: Hume and Nattrass¹² recorded 45 per cent cured, Magnus-Alsleben¹⁶ 40 per cent and Longcope¹⁴ 41 per cent.

In the present series of sixty-six patients followed for an average period of observation of 123 days, only eight (12 per cent) recovered while under observation. Another probably recovered but had persistent hypertension. The remainder were evacuated while still showing evidence of disease. There were no deaths. Of those who recovered one-half did so within one month, the other one-half within two to six months. Sixteen patients (24 per cent) had achieved normal renal function and were free from granular casts by the time they were evacuated. However, residual albuminuria, usually with slight microscopic hematuria, was still present. The remaining forty-one patients (62 per cent) were considered probable candidates for chronic nephritis. All had persistent granular casts and raised E.S.R.; renal function was impaired in thirty-two. Details are given in Table v.

A follow-up study is being carried out. So far, subsequent progress has been reported in twelve patients. Of five evacuated as probably chronic cases, two were much the same six months later but three had improved; of seven evacuated with residual albuminuria, with or without red cells in the urine, three recovered within six months and four were much the same.

The unfavorable outlook in this series, however, does not reflect the true prognosis of acute nephritis in this group for these patients were investigated at a base hospital and many were transferred to it because they were severely ill or did not recover quickly. Reports on prognosis from forward hospitals appeared more favorable.

There was no substantial difference in age between those who recovered while under observation and those who were evacuated with persisting signs of renal disease. Contrary to the opinion of Fishberg³ the degree of hypertension was less important than its duration; very high pressures were observed in some who recovered or who had nearly

recovered when evacuated; when hypertension lasted more than a month, however, the subject rarely did well. (Fig. 6.) The duration rather than the degree of early edema had a similar significance.

TREATMENT

While it is doubtful whether any treatment administered had any influence on the

acute glomerular block is due to vascular spasm rather than to structural change. Otherwise it is doubtful if any material benefit resulted from dietetic restrictions. Moderate reduction of protein and fluid had little demonstrable effect nor did an increase influence the course adversely.

Bed Rest. During the acute phase of the disease bed rest appeared to be essential

TABLE V
STATE OF PATIENT WHEN DISCHARGED OR EVACUATED

Result	Time in Months						Total	Per cent
	1	2	3	4	5	6		
Cured.....	4	1	1	1	..	1	8	12.1
Residual proteinuria; sedimentation rate normal.....	4	2	6	4	16	24.2
Proteinuria; sedimentation rate abnormal; renal function good.....	3	1	2	6	9.1
Nephritic urine; renal function impaired.....	1	2	3	7	12	4	29	43.9
Nephritic urine; renal function good; edema.....	1	..	1	2	
Nephritic urine; renal function impaired; edema.....	1	1	
Nephritic urine; renal function good; hypertension.....	..	1	1	
Nephritic urine; renal function impaired; hypertension.....	1	1	..	2	
Nephritic urine; renal function impaired; edema; hypertension.....	
Edema only.....	1	1	
Hypertension only.....	1	1	

final outcome of the disease, certain transient effects were observed which have a direct bearing on pathogenesis.

Period of Absolute Starvation. As soon as the diagnosis was established the patient was put to bed on absolute rest and all food and fluid were withheld for forty-eight to sixty hours routinely. This measure appeared to initiate diuresis, reduction of edema and subsidence of hypertension. A similar but less pronounced and less constant effect resulted from rest alone without the rigid dietetic restriction. Simultaneously, the glomerular filtration rate rose sharply in some patients to average or high normal levels during the fast but returned to its previous figure soon afterward. This behavior is opposite to that of normal controls under similar fasting conditions when filtration drops markedly and therefore indicates temporary relief from glomerular block. An effect so transient and sudden as this suggests that in cases in which it occurred

only as long as edema and hypertension were present. After these have disappeared we have often seen proteinuria and the number of red cells in the urine increase in patients in whom the E.S.R. was still accelerated. In two of these patients granular casts reappeared and in three concentrating power deteriorated. There is no evidence, however, that this means aggravation of the disease.

Penicillin. Moncrieff¹⁵ and Suchecki¹⁶ suggested that penicillin was beneficial in the treatment of early acute glomerulonephritis by eradicating responsible foci of infection. Although a diligent search for persistent foci of infection was made in all patients in this series and few were found, it was decided to give penicillin a trial in order to test the truth of the general belief that such foci play some part in determining the course of the disease. Twelve patients were selected for this purpose. They had been ill for four to twelve weeks and their

condition was relatively fixed. Penicillin was administered intramuscularly in doses of 15,000 units every three hours to a total of 700,000 to 900,000 units. The only demonstrable effect was further acceleration of the E.S.R. at the completion of the course. The reason for this was not clear.

COMMENTS

Analysis of the data available from this group of patients with acute glomerulonephritis makes it possible to speculate on the pathogenesis of the disease.

The disease is obviously related to a previous infection, not necessarily streptococcal, the incidence of which in our series was almost identical with that of Longcope.¹⁴ The interval of 16.5 days between the beginning of the infection and the first evidence of the disease is about a week longer than that in serum sickness, but our observation on the patient with vascular nevus suggested that the true interval might well be a week shorter; it resembles the interval which separates rheumatic fever and allied disorders from the preceding infection. The occurrence of rheumatic fever, Schoenlein-Henoch purpura and urticaria in about 10 per cent of our patients indicates that the etiologic factors in all these diseases may be similar. These conditions occurred infrequently alone among our hospital admissions, which makes this suggestion still more probable. An allergic basis is currently thought to be responsible for the latter diseases and experimental evidence in favor of an allergic origin for acute glomerulonephritis is steadily increasing.¹⁷⁻²⁰

The morphologic substrate of an allergic reaction consists of a capillary lesion²¹ and smooth muscle spasm.²² The first manifestations of acute glomerulonephritis, occurring usually when the previous infection has subsided, appear to be the result of a widespread capillary lesion and arteriolar spasm. Glomerular obstruction, hypertension and edema usually occur simultaneously, yet we believe we have demonstrated that these are independent of each other

and each has its own mechanism of origin. The evidence in favor of a generalized vascular reaction, independent of the renal process, is extensive. There can be no doubt, for example, that early edema does not depend upon renal insufficiency; thus it may precede all other evidence of nephritis by several days, as has been pointed out by Henoch,²³ Nonnenbruch,²⁴ Volhard²⁵ and others and it may occur, as in the cases of Guggenheimer²⁶ and in Case 18 of this series, without any renal involvement whatever; proof suggesting its dependency upon a capillary change was provided by the behavior of our patient with vascular nevus. Again, transient hypertension may occur without demonstrable renal involvement as shown in Case 18, and Pickering²⁷ has concluded that it is probably not renal in origin. He found that it behaved differently from the hypertension of chronic nephritis and did not appear to depend upon humoral mechanisms but upon a neurogenic one. While we do not question the importance of the renal element in the origin of hypertension of late renal disease, it is still unsettled what role it plays in the acute phase.

The glomerular capillaries are, of course, usually the site of severe morphologic changes, similar to those produced by Frochlich²¹ in the capillaries of a frog mesentery. However, we have drawn attention to the fact that sometimes under the influence of complete starvation and thirst diminished glomerular activity may suddenly be reversed, to reappear with cessation of the starvation period. We think that this phenomenon can be explained if we assume that in addition to the morphologic component there is also spasm of the afferent arteriole which can be reversibly influenced through some dietary mechanism not yet clearly understood. If a sufficient number of glomeruli are thrown out of action, filtration is seriously reduced and retention of non-protein nitrogen follows.²⁸ Albuminuria is due to increased capillary permeability and hematuria provides gross evidence of capillary damage and may be the renal counterpart of petechiae in the ocular

fundus and skin. In view of the frequency of hematuria the rarity of systemic petechiae requires some explanation. Perhaps the discrepancy depends on the fact that the glomerular capillary pressure is greater than the pressure in the systemic capillaries. The renal tubules are necessarily affected by the vascular lesion involving the tufts and they may be further handicapped by vascular alterations in the afferent arterioles and tubular capillaries.

This hypothesis provides an acceptable explanation for the early manifestations of acute glomerulonephritis and makes understandable the occurrence of various clinical types and the independent behavior of the clinical manifestations. When systemic vessels are chiefly involved, hypertension and edema overshadow glomerular and tubular dysfunction or may even occur alone; if arteriolar spasm is more pronounced than increased capillary permeability, hypertension overshadows edema and vice versa. On the other hand, when the renal vessels are chiefly involved, hypertension and edema are less pronounced than renal lesions or may be absent altogether; if spasm of the afferent arterioles dominates the disorder, acute diminution of glomerular activity with impaired filtration and retention of non-protein nitrogen dominates the clinical picture; if spasm is less pronounced than simple damage of the capillary wall, hematuria and albuminuria are more conspicuous. It is not to be expected that conditions causing acute diminution of glomerular activity would not also profoundly alter the behavior of the glomerular capillaries and renal tubules so that reduced filtration with retention of non-protein nitrogen could hardly occur without hematuria, albuminuria, impaired concentration and cylindruria. On the other hand, damage to the glomerular capillaries could well occur without reducing filtration and without interfering with tubular function.

The hypothesis is adequate to account for the initial or acute stage of the illness. In the section dealing with the course of the disease we have shown that this stage lasts usually

less than a month. Its end is marked by disappearance of edema, subsidence of hypertension and signs of diminished glomerular activity and in the most favorable cases also by disappearance from the urine of those abnormal elements indicative of a lesion of the glomerular capillaries. In the majority of patients, however, recession of some of the renal manifestations, namely, of albuminuria, microscopic hematuria and of the impaired concentrating power, is less prompt and these signs may be indicative of a subacute or chronic course. The idea that a persistent focus of infection is responsible for perpetuating an allergic renal reaction⁸ is hardly tenable, except in isolated instances, because the manifestations which are most likely to be allergic are those which are not so perpetuated; again, persistent foci of infection are rarely found in those cases and penicillin in no way influences their course.

The question at issue is whether the allergic process behaves differently in the kidneys than in other tissues, or whether it subsides as elsewhere but, owing to peculiar conditions, leaves changes in the kidneys which tend to be irreversible. The enclosure of the swollen organ in the tough, unyielding capsule might be one of the reasons why the acute process leaves greater residual damage in the kidneys than in other tissues. It should be borne in mind that the pressure in the glomerular capillaries is much higher than capillary pressure elsewhere and consequently a slight residual impairment of the capillary wall, which in other parts of the body could not be detected, may manifest itself in the kidneys by albuminuria and hematuria. Our cases of the nephrotic syndrome, which developed without a gap from the acute stage, suggest that a chronic capillary lesion due to some undetermined mechanism may be the underlying fault. This possibility would avoid the necessity of invoking a dual origin of edema, continuing without interruption in the same patient.

The comprehension of a persisting tubular lesion which, according to the hypothesis

previously stated, is regarded as secondary to vascular events and might be expected to clear up soon after the renal vessels regain their normal function is more difficult. We have observed, however, several cases of sulfonamide obstruction of both ureters lasting for twelve to twenty-four hours, in which all symptoms and signs quickly subsided after removal of the obstruction by ureteral catheterization, with the exception of impaired power to concentrate urine which persisted for three to eight weeks. It seems, therefore, that the renal osmotic function not only can suffer very easily but once disturbed requires considerable time under ideal conditions to recover. Yet conditions in a convalescent from acute nephritis often are not ideal; as was pointed out in connection with the endogenous creatinine clearance, glomerular filtration often remains in this stage on the low side of the normal and its variations tend to disappear, suggesting a residual restriction of the glomerular surface.

The hypothesis then accounts for all the features and varieties of the syndrome if it is admitted that under certain circumstances an allergic lesion can produce changes which may persist. The concept of an allergic lesion which persists or even progresses long after subsidence of the acute infection which initiated it is not a new one. Subacute and chronic polyarthritis, initiated by streptococcal, gonococcal, dysenteric or other acute infection is believed by some to represent similar allergic behavior; indeed there is reason to suppose that the problem of chronic nephritis and that of chronic polyarthritis may be related. Many varieties of allergic dermatitis persist long after all traces of the provocative allergens have been removed from the system, while in some cases another factor is known to be responsible for perpetuating the disorder, for example, sunlight in sulfonamide dermatitis.

SUMMARY AND CONCLUSIONS

1. A clinical study of sixty-six patients with acute glomerulonephritis is presented:

the average period of observation was 123 days.

2. The course was divided into two distinct phases: The first rarely lasted more than a month, the fully developed picture consisting of hypertension, edema, acute diminution of glomerular activity with retention of non-protein nitrogen and a rapid E.S.R., hematuria and albuminuria, accompanied by impaired concentration and the appearance of casts. The second showed a pronounced tendency to chronicity and was characterized by the absence of hypertension, edema or retention of non-protein nitrogen, but by the persistence of albuminuria, microscopic hematuria, impaired concentration, cylindruria, slight or moderate acceleration of the E.S.R. and also some restriction of the normal fluctuations of glomerular filtration.

3. The occurrence of partial syndromes suggested that the term acute glomerulonephritis is a misnomer; thus there were patients with transient hypertension and edema with little or no evidence of renal involvement; others with no extrarenal manifestations but with reduced filtration, hematuria, albuminuria, impaired concentration and granular casts and others with edema and albuminuria only, or associated with minimal red cells in the urine or with slight impairment of concentration (the nephrotic syndrome). The great majority were mixtures in varying proportions of these three types.

4. The hypothesis that the syndrome called acute glomerulonephritis is a generalized vascular reaction of the allergic type to streptococcal and probably other infections is discussed. In this view transient hypertension and edema are regarded as extrarenal manifestations due to general arteriolar spasm and to increased capillary permeability, respectively. Their respective renal equivalents appear to be acute diminution of glomerular activity with retention of non-protein nitrogen due to gross spasm of the afferent arterioles, as well as swelling of the glomerular endothelial cells and exudation in Bowman's space and pro-

teinuria. The chronic proteinuria, and possibly chronic edema in some cases, developing without interruption from the acute stage are believed to represent persistence of the capillary lesion.

5. A forty-eight-hour period of complete food and fluid starvation appeared to exert a transient beneficial effect on hypertension, edema and glomerular activity. Penicillin in no way appeared to alter the course of the disease.

6. When hypertension and edema lasted for more than one month, irrespective of their degree, the subsequent course of the illness was nearly always prolonged, which suggests that a certain number of patients in this series subsequently progressed into the chronic phase of the disease.

Acknowledgments: This investigation was made in the 103rd British General Hospital in an active theater of war, and it was possible only by the interest and cooperation of Lieut. Colonel Paul Wood. Grateful acknowledgment is made to Professor Homer W. Smith and Drs. William Goldring and Herbert Chasis for fruitful suggestions, and to the British War Office for permission for publication.

REFERENCES

1. POPPER, H., MANDEL, E. and MAYER, H. Zur Kreatininbestimmung im Blute. *Biochem. Ztschr.*, 291: 354, 1937.
2. POPPER, H. and BROD, J. Die physiologischen Schwankungen der Nierenarbeit. *Ztschr. f. klin. Med.*, 134: 196, 1938.
3. FISHBERG, A. M. Nephritis and Hypertension. Philadelphia, 1939. Lea and Febiger.
4. WALKER, A. M., BOTT, P. A., OLIVER, J. and MACDOWELL, M. C. Collection and analysis of fluid from single nephrons of mammalian kidney. *Am. J. Physiol.*, 134: 580, 1941.
5. SMITH, H. W. The Physiology of the Kidney. New York, 1937. Oxford University Press.
6. SHANNON, J. A. The control of the renal excretion of water; effect of variations in state of hydration on water excretion in dogs with diabetes insipidus. *J. Exper. Med.*, 76: 371, 1942.
7. SMITH, H. W. Lectures on the Kidney. University Extension Division, University of Kansas, Lawrence, Kansas, 1943.
8. HOLTEN, C. and REHBERG, P. B. Studies on the pathological functions of the kidneys in renal disease. *Acta med. Scandinav.*, 74: 479; 583, 1931.
9. EARLE, D. P., JR., TAGGART, J. V. and SHANNON, J. A. Glomerulonephritis. *J. Clin. Investigation*, 23: 119, 1944.
10. CHASIS, H. and SMITH, H. W. The excretion of urea in normal man and in subjects with glomerulonephritis. *J. Clin. Investigation*, 17: 347, 1938.
11. GOLDRING, W. and CHASIS, H. Hypertension and Hypertensive Disease. New York, 1944. The Commonwealth Fund.
12. HUME, W. F. and NATTRASS, F. J. The late effects of war nephritis. *Quart. J. Med.*, 21: 1, 1927.
13. MAGNUS-ALSLEBEN, E. Ueber die Folgezustände der Kriegsnephritis. *Deutsche med. Wchnschr.*, 54: 1914, 1928.
14. LONGCOPE, W. T. The pathogenesis of glomerular nephritis. *Bull. Johns Hopkins Hosp.*, 45: 335, 1929.
15. MONCRIEFF, A. Penicillin in acute nephritis. *Lancet*, 2: 247, 706, 1944.
16. SUCHECKI, A. Penicillin in acute nephritis. *Lancet*, 1: 248, 480, 1945.
17. SCHICK, B. Die Nachkrankheiten des Scharlach. *Jahrb. f. Kinderh.*, 65: 132, 1907.
18. LUKENS, F. D. W. and LONGCOPE, W. T. Experimental acute glomerulitis. *J. Exper. Med.*, 53: 511, 1931.
19. MASUGI, M. Zur Pathogenese der diffusen Glomerulonephritis als allergische Erkrankung der Niere. *Klin. Wchnschr.*, 14: 373, 1935.
20. RICH, A. Hypersensitivity in disease. Harvey Lectures. Pp. 106-147. Lancaster, Pa., 1946-1947. Science Press.
21. FROELICH, A. Ueber lokale gewebliche Anaphylaxis. *Ztschr. f. Immunitätsforsch. u. exper. Therap.*, 20: 476, 1914.
22. ROESSLE, R. Allergie and Pathergie. *Klin. Wchnschr.*, 12: 574, 1933.
23. HENoch, E. H. Ueber Nephritis scarlatina. *Berlin klin. Wchnschr.*, 10: 597, 1873.
24. Nonnenbruch, W.: Ueber extrarenale Oedemgenese und Vorkommen von konzentrierten Blut bei hydropischen Nierenkranke. *Ztschr. f. klin. Med.*, 136: 170, 1921.
25. VOLHARD, F. Die doppelseitigen haematogenen Nierenerkrankungen. Handb. d. inn. Med. Berlin, 1931. Bergmann and Staehelin.
26. GUGGENHEIMER, H. Das Verhalten von Herz- und Gefäßsystem bei der akuten diffusen Glomerulonephritis der Kriegsteilnehmer. *Ztschr. f. klin. Med.*, 86: 225, 1918.
27. PICKERING, G. W. Observations on the mechanism of arterial hypertension in acute nephritis. *Clin. Sc.*, 2: 363, 1935.
28. BROD, J. Clinical significance of filtration and reabsorption in the kidneys. (English summary.) *Časop. lél. česk.*, 85: 1315, 1946.

Pulmonary Adenomatosis*

SYLVIA BUBIS, M.D. and JAMES H. ERWIN, M.D.

Columbus, Ohio

PULMONARY adenomatosis, or infectious adenomatosis, is a rare, chronic, irreversible condition consisting of hyperplasia and metaplasia of the alveolar epithelium into tall columnar mucus-producing glandular tissue. Histologically it is benign but involves both lungs, eventuating in complete loss of respiratory function and death by asphyxia. Clinically its onset may start with an acute respiratory infection which never clears completely. Its course is marked by frequent superimposed pulmonary infections for which antibiotics only temporarily relieve the respiratory embarrassment and increase the vital capacity. It has been noted only in adults, with the possible exception of the case of a seventeen year old girl reported by Geever, Carter, Neuberger and Schmidt.¹³ The disease has been found in Germany, China, Canada and the United States, cases being discovered with increasing frequency. The etiology has been undetermined but is believed by many to be a virus infection.

A similar disease in animals, chiefly in sheep, was first reported in 1891 by Eber, in Germany, according to Sims.²⁴ Bonne³ states that Roux, in 1903 in France, described these lesions in sheep suffering from sheep pox and that Spronek discovered similar lesions in guinea pigs in 1907. Richardson²¹ and Bell² give Helly credit for describing the first human case of pulmonary adenomatosis in Germany in 1907. His patient was a forty-three year old woman with "symptoms of tuberculosis." The following year Löhlein²¹ recorded in the German literature an instance of a disease involving the right upper lobe and which was productive of a large amount of mucus. Adenomatosis of the lungs in mice,

horses and rabbits has also been reported. In sheep in South Africa the disease is known as jaagsiekte.

Cowdry⁵ and Cowdry and Marsh⁶ described the disease as a specific endemic, chronic, catarrhal pneumonia which was fatal in two to eight months. They postulated that epithelial proliferation was secondary to thickening of the interalveolar tissue. There was little or no fever but marked respiratory distress, nasal discharge, cough, rales, weakness, weight loss and anemia. The gross and microscopic findings in sheep were identical with those found in humans. Dungel, cited by Bell² and Bonne,³ described the disease in sheep in Iceland, proved its contagiousness and called it epizootic adenomatosis. It is probably similar to verminous pneumonia and Montana progressive sheep pneumonia. M'Fadyean,³ Bonne,³ Theiler,³ Straub,²¹ DeKock,³ Richardson²¹ and Geever et al.,¹⁰ who reviewed the studies of Bosc, Borrel, Thorp, Hallman, Davis, Robertson, Osenkop and Furth, also reported the disease occurring naturally in animals. More recently Norris¹⁹ found the disease in a guinea pig inoculated with pleural fluid from a patient convalescing from pneumonia. The patient had no evidence of the disease and this was thought to be a spontaneous occurrence.

The pathogenesis of abnormal pulmonary alveolar lining has been the subject of a great deal of controversy. We may consider the problem from several different aspects: (1) failure of normal development, (2) stimuli which excite abnormal proliferation and (3) experimental production of abnormal alveolar epithelium. Normal alveoli in early fetal life appear glandular and

* From the Department of Pathology, White Cross Hospital, Columbus, Ohio.

are lined by a cuboidal epithelium thought by most investigators to be of entodermal origin, according to Maximow and Bloom.¹⁶ In the human embryo of 170 mm. the continuous epithelium becomes interrupted by blood vessels, eventually leaving the epithelium as isolated round cells and the capillary walls exposed to air. Zeldes³¹ has shown that during the twenty-fourth to thirty-third week of intra-uterine life the transition to the adult type of alveolar lining occurs. The mechanism of this transition is said to be by a disintegration of nuclei, degeneration of cytoplasm and casting-off of the cells or by encroachment of capillaries and desquamation of the epithelium. Persistence of the large cuboidal cells, Zeldes demonstrated, is not compatible with respiration and therefore with life and has been found to be persistent in 50 per cent of "viable" premature infants and in 20 per cent of full-term infants. Reviewing our autopsies of premature and full-term infants with "failure of lung expansion," we found persistence of cuboidal epithelium frequently and aspiration of amniotic fluid and cells as the other common cause; occasionally we found the two together.

The work of el Gazayerli⁹ and others rather conclusively demonstrates the origin of the alveolar phagocyte which is of importance because of the association of phagocytes with adenomatosis and the infrequent mitotic figures seen in these instances. These observers demonstrated that the cuboidal cells which are located in the angles of the alveolar spaces give rise by mitosis to the free alveolar phagocytes. By injection of trypan blue these cells have been shown to phagocytize the dye, as do other cells of the reticulo-endothelial system, while the other flattened polygonal alveolar epithelial cells do not.

In the fully developed lung certain stimuli have been found which excite abnormal proliferation, hyperplasia and metaplasia. The excellent descriptions of Bell² and of Geever et al.¹⁰ include: (1) chronic passive congestion associated with

old mitral or aortic valve disease, (2) infectious diseases of the lungs, particularly when a chronic interstitial pneumonia results, (3) lung adjacent to nodules of chronic granulomas, tuberculosis, silicosis, syphilis and to (4) old empyema pockets, (5) old pleuritic adhesions, (6) chemical pneumonia, (7) lipid pneumonia, (8) other aspiration pneumonias, (9) war gases such as phosgene, (10) physical agents such as x-rays and radium, (11) lung adjacent to benign and malignant neoplasms and (12) toxoplasmosis. Chronic anoxia, with loss of alveolar function due to thickening of the interalveolar septa or to filling of alveoli with foreign material, appears to be the basic cause of the disturbance. It has been suggested that bronchial epithelium grows down into the alveoli, but numerous transition stages indicate that the epithelium develops from cells already present. A vicious cycle is set up, with the thickening of the alveolar septa and viscid mucus preventing oxygen from reaching the capillaries and stimulating alveolar epithelization with cuboidal to mucus-producing columnar cells.

Similar changes in alveolar epithelium have been produced experimentally. Young³⁰ produced diffuse epithelial proliferation in the lungs of rabbits consistently with optimum concentrations of various electrolytes. The alkali metals, Li, Na and K and the alkaline earth metals Mg, Ca and Sr, were found effective only in strong solutions. The trivalent metals, Al, La and Fe, were efficient, and the heavy metals were effective in weak solutions, the order of their efficiency being Hg, Ag, Cu, Cd, Pb and Zn. Grady and Stewart¹⁴ induced pulmonary tumors of this nature in strain A mice, using subcutaneous injections of 1,2,5,6-dibenzanthracene or methylcholanthrene in lard suspensions and using lard as controls. Five weeks after injection tumors began to appear, practically all growths of alveolar origin and not associated with inflammatory reaction. In many instances there was no distortion of pulmonary architecture, alveolar lumens remaining

TABLE I
PULMONARY ADENOMATOSIS

Observer	Year	Age	Sex	Nationality	Symptoms	Duration	Urine	Blood	Mitoses	Invasion	Description of Lung
1 Helly	1907	43	F	German	Symptoms of tuberculosis						
2 Lohlein	1908			German	Abundant mucus						
3 Bonne	1939	31	M	Chinese	Fever, persistent cough, mucus, dyspnea, emaciation	9 mo	Negative	Negative	Fairly numerous	Yes, no metastases	Right upper lobe Weight 2,700 Gm, bilateral disease, moist, pale, friable tumor nodules
4 Richardson	1940	73	F	American	No symptoms of lung disease, died of obstructive jaundice, stone in common duct		Bilirubin				Small, firm, scattered nodules, 2-10 mm, bilateral all lobes
5 Taft and Nickerson	1941	62	M	American	Pleurisy, cough, fatigue, mucus sputum, weight loss, dyspnea, cyanosis, fever, tuberculin test slightly positive	8 mo		White blood cells elevated			Weight 700 and 850 Gm, several small areas of cavitation 0.4 to 1.5 cm
6 Taft and Nickerson	1943	79	F	American	Pernicious anemia in relapse, increasing pulmonary infections, diverticulosis, cholelithiasis			Type vir pneumococcus, hemolytic staphylococcus			Weight 420 and 700 Gm bilateral disease
7 Bell	1943	63	M	American	Dyspnea, cough, weakness, weight loss, mucus sputum	2 yr	Negative	Negative			Heavy lungs, firm, solid homogeneous tumors
8 Sims	1943	42	M	American	Dry cough early, then mucus sputum, pain, weakness, fever, cyanosis, clubbed fingers	2 yr		White blood cells elevated later 3,700	Occasional		
9 Oberndorfer	1930	21			Septic hemorrhagic pneumonia						Bilateral, dark red, one apex free
10 Wood and Pierson	1942	57	F	American	Fatigue, night sweats, cough, developed carcinoma of cervix after lobectomy	2½ yr	Negative	Negative	Infrequent	None	2.0 cm cavity, 0.1 cm nodules, one lobe removed surgically
11 Alexander and Chu	1947	56	F	American	Fever, pleuritic pain, cough, sputum, dyspnea, cyanosis	5½ yr	Albumin, red blood cells	Hb 11, positive Wassermann	None	None	Weight 2,100 Gm, necrosis resembled Friedländer's infection, green, gelatinous, also had pancreatic island adenoma
12 Reinhardt (O S U)	1946	This patient was seen by us, but the case has not been reported									Voluminous lungs, bilateral disease
13 Paul and Ritchie	1943	68	F	American	Severe dyspnea for 6 mo, cough, small amount frothy sputum, weight loss, cyanosis	6-8 yr		White blood cells 32,400	?	Yes	Extensive pneumonia bronchiectatic cavities, largest 7 cm
14 Paul and Ritchie	1945	52	M	American	Increasing dyspnea, weight loss, cyanosis	2½ yr					Left lung granular, nodular, bronchiectasis, acute and organic pneumonia? more active,? malignant
15 Paul and Ritchie	1943	60	F	American	No pulmonary complaints, carcinoma of pancreas, metastases to liver, gallbladder						Bronchiectasis, atelectasis, emphysema, acute and organic pneumonia, one local area with obvious benign proliferation of bronchial epithelium
16 Paul and Ritchie	Unpublished, similar										
17 Simon	1945	70	F	Canadian	Cough, thick white mucus Dyspnea, orthopnea, cyanosis, emaciation	7 wk			0	0	Obliteration of right thorax, dense adhesions, band of consolidation, elevation, granular, sticky, all lobes
18 Simon	Unpublished, but similar										
19. Geever et al	1943	17	F	American	Cough, fever, weight loss, dyspnea, cyanosis	13 mo			Rare		Obliteration of pleural cavity, diffuse gray nodular tumors, pinhead to 1 cm size, columnar mucus product, occasional pseudostratified and papillar proliferation
20 Fidler, Erwin and Bubis	1946	66	M	American	Chest pain, severe to moderate cough, yellow mucus sputum, cyanosis	Moderate cough for several yr		White blood cells 20,300	Few	None	1,370 Gm each, firm, pale solid nodules
21 Fidler, Erwin and Bubis	1946	63	M	American	Same as above, plus severe emaciation and weakness			White blood cells 18,000 slight anemia			Same as above

patent and the walls lined by cuboidal cells producing a glandular appearance. There was no connection of these tumors with bronchi. There were some solid nodules of tumor tissue and a few mitotic figures but no evidence of malignancy. Geever et al.¹⁰ report that Wells, Slye, McDonald and Woodhouse, Holmes, Andervont, Breedis, Robertson, Osenkop and Furth produced similar lesions with tar as did Simonds and Curtis.²³ Bell² states that Grumbach found glandular epithelium developing in guinea pigs with experimentally produced pneumonia.

There is some support for the suggestion of Cowdry and Marsh⁶ that pulmonary adenomatosis is incited by a virus. Straub²⁵ found adenomatosis in mice infected with influenza virus. Bonne² states that Theiler thought the disease in horses was due to a poisonous plant, *Crotalaria dura*. Dungall reported associated nematodes in the lungs of sheep, and DeKock thought it a neoplasm found in sheep. Many others believe it a neoplasm and describe similar cases, differing only in that they found regional, brain and bone metastases. However, Taft and Nickerson²⁷ conclude in reporting their two cases that "this condition is of but little significance in the genesis of pulmonary carcinoma in general."

We are presenting two cases of patients with benign pulmonary adenomatosis autopsied at the White Cross Hospital, Columbus, Ohio, in 1946. Nineteen cases have been found in the literature to date. The ages range from seventeen to seventy-nine. Geographical distribution and occupation varied widely. No contact with any infected animal was recorded. Most of the patients had in common a prolonged history of at least eight months' duration, apparently following an acute pulmonary infection which did not clear up entirely. The blood and urinary findings were usually normal. Fever, malaise and leukocytosis when present were remittent in character depending upon secondary infections. Cough productive of copious mucoid sputum was almost universal. The sputum was negative for

acid-fast organisms or any other constant invader and the tuberculin test when done was negative or only slightly positive. Weight loss, weakness, severe dyspnea and cyanosis were also present. In only one case was clubbing of the fingers described. Although there was chronic lung disease over long periods, cor pulmonale was not noted. Two patients had no symptoms of lung disease at all, one case reported by Richardson²¹ and one by Paul and Ritchie.²⁰ The immediate cause of death was anoxia or sepsis from acute pulmonary infection except in Richardson's patients who died of obstructive jaundice due to a stone in the common duct, Wood and Pierson's²⁹ patient who died of metastatic adeno-acanthoma of the cervix and one of Paul and Ritchie's patients who died of carcinoma of the pancreas with regional metastases. One of Taft and Nickerson's²⁷ patients also suffered from pernicious anemia in relapse, associated with increasing pulmonary infection and bacteremia. The gross and microscopic pictures were all similar, with the possible exception of those of Paul and Ritchie,²⁰ one of Geever, Carter, Neuberger and Schmidt¹³ (who emphasized the radiologic findings and only briefly described the gross and microscopic findings) and one case of Simon²² which has not yet been reported but is said to be similar.

Pulmonary lesions similar to those of infectious adenomatosis but with metastatic lesions have been reported by Sweany,²¹ recording cases of Wolf, Kretchmer, Pèpère, Morelli, Perls, Fuchs, Tillman, Grunwald, Briese, Domeny, Oberdorfer, Knierim, Salitykow, Ribbert, Chiasi, recorded by Bonne³ and by Kaufman, Letulle, Weisman, Rous, Frissell and Knox in the paper by Neuberger.¹⁸ Most metastases were to regional lymph nodes but occasional sites were found in the bones, liver and brain. Cassilli and White, according to Neuberger,¹⁸ reported a case which they named "carcinomatoides alveogenica multicentrica," in which the lesion was confined to the lung sacs and did not invade the septa or bronchi nor did it metastasize. Geever, Neuberger and Davis¹²

listed five cases which they believed were malignant. In neither of our cases was there invasion, metastasis or evidence of malignant change.

CASE REPORTS

CASE 1. A white male, sixty-six years old, was admitted to the medical service March 26, 1946, with the chief complaint of pain in his chest for three months. Three months prior to admission the patient had pneumonia from which he had never made a complete recovery. He had been ambulatory only for a brief period of one week. Since the onset of his illness, he had had intermittent fever without chills, a severe cough accompanied by the production of a yellowish mucous sputum and left chest pain which was aggravated by coughing. The past history revealed that he had never been entirely free from a cough for the past several years of his employment as a molder. Other complaints were non-contributory. On admission his temperature was 101.2°F., pulse rate 96, respiration 94 and blood pressure 125/88. Physical examination revealed a well developed, well nourished white male of stated age. The essential findings were those limited to the chest. There were accentuated breath sounds, with a friction rub and dullness to percussion in the lower portions of each lung. No other significant findings were reported.

Laboratory examination of the urine was negative; hemoglobin, 16 Gm.; red blood cells, 5,300,000; white blood cells, 20,200 with 88 per cent polymorphonuclear cells. Clinical impressions were silicosis, pneumonitis and possible lung abscess.

X-rays of the chest taken on March 7, 1946, revealed no apparent abnormalities of the heart and aorta; the upper third of each lung was clear. Mid- and basal linear markings were intensified bilaterally, with a considerable amount of pneumonitis in these areas. It was thought that there were several small cystic areas in both bases, with the addition of a slight amount of left pleural fluid. On March 29, 1946, lipiodol instillation indicated a sacular bronchiectasis in the basal portion of each lung, more marked on the right and anteriorly.

Sulfadiazine therapy was started but was later changed to penicillin; there was a resultant drop in temperature to 97.2°F. within twenty-four hours. The temperature remained at normal levels for three days, during which time peni-

cillin was continued. Because of a rise in temperature at the end of this period, sulfadiazine therapy was given again. There was a temporary response but on the eighth hospital day the patient became progressively worse, semi-comatose and had to be restrained. Respirations were harsh and labored and the pulse feeble. Death occurred as the temperature rose to 104.6°F.

When the chest was opened at autopsy, both lungs were found to meet in the midline anteriorly and to completely obscure the cardiac area. The lungs were bound to the chest wall by old, dense, pleural adhesions which could be separated only with difficulty. The left lung weighed 1,370 Gm. The upper lobe was partly crepitant while the lower lobe was denser and mottled. Upon dissection of the tracheobronchial tree the left bronchus was found to be slightly narrowed in its lower division and contained a slight amount of thin whitish exudate. The cut surface showed a diffuse anthracosis and no cavities. The lower lobe showed a mottled greyish-yellow consolidation about which the deeply anthracotic lung slightly retracted, causing these areas to appear elevated above the cut surface. Again, a thin, purulent fluid could be expressed. The lung contained no evidence of malignancy or tuberculosis. A few similar scattered, shot-like areas appeared throughout the upper lobe. The right lung was similar to the left except that its bronchial tree showed no evidence of atelectasis and the upper lobe contained only a few small areas of inflammatory reaction. The middle and lower lobes were largely fused by pleural adhesions and their cut surfaces were also extensively mottled and grossly similar to the other lobes. The peribronchial and hilar lymph nodes were quite hard, elastic and of a deep black color.

Microscopic sections from the right and left lungs showed an entirely similar picture, consisting of chronic congestion and moderate anthracosis throughout the upper lobes, with small areas of inflammatory reaction similar to that found diffusely throughout the lower lobes. In these lobes there was a process quite similar to a partially organized pneumonia in which the alveoli were filled with a fibrino-purulent exudate but showed only slight fibrinous organization with a subacute exudate filling the alveoli. The alveolar lining cells showed a process of proliferation and metaplasia producing a benign adenomatosis in which some

alveoli were lined by hyperplastic cells while others were widened and distended with a mucous secretion. The cells lining such alveoli tended to a columnar form, sometimes showing a globular secretion. This process could be traced from alveoli in which no such reaction was present, except for the presence of some pneumonic exudate, through those in which there was slight to moderate alveolar epithelial hyperplasia, to those just described in which the alveoli varied from solid to cystic. In such cystic areas the exudative reaction largely disappeared. The process was that of adenomatosis. There was no evidence of tuberculosis or silicosis. The pleurae showed a marked chronic fibrous thickening. The hilar lymph nodes showed no recent inflammatory reaction but were replaced by a sclerotic type of fibrosis, together with anthracosis and slight calcification.

CASE II. A sixty-three year old white male was admitted to the medical service on October 9, 1946, with the chief complaint of coughing and shortness of breath for five years. These symptoms had gradually progressed, with recurrent bouts of coughing and fever which were largely relieved by intensive chemotherapy but which would recur when such treatment was discontinued. Dyspnea had increased during the past year without paroxysms and without orthopnea or pedal edema. The cough was relieved when the patient lay on his left side but was aggravated when lying on his back or right side. In August, 1946 repeated chest films, including lipiodol injection, showed a patchy opacity throughout the lower three-fourths of the right lung and in the mid-portion of the left lung there were numerous patchy nodular areas accompanied by increased bronchial markings. The process was thought to be of granulomatous character. Repeated examination of the moderate amounts of sputum which were being produced at that time revealed a number of Friedländer's bacilli and a few diphtheroids but no fungi could be demonstrated on direct smear or culture.

Upon admission the blood showed hemoglobin, 10 Gm.; red blood cells, 3,500,000; white blood cells, 18,000 with 90 per cent polymorphonuclear neutrophils. The temperature was 100.2°F., pulse 84, respirations 20 and blood pressure 110/70. Physical examination revealed a weak, emaciated, moderately cyanotic white male. Examination of the chest disclosed marked dullness at the right base extending up to the

fourth rib posteriorly. Breath sounds were normal except over this area where they were of marked bronchial character. The whispered voice was clearly transmitted over this area and fine and coarse rales were heard above this region. The heart was thought to be slightly enlarged to the left.

X-rays of the chest showed a patchy opacity throughout the lower three-fourths of the right lung and a large area of consolidation in the mid-portion of the left, with apparently many fibrous strands along the line of the bronchial trunks in the lower half of the left lung. The radiologist's impression was that the process was a granulomatous one probably caused by a fungus.

After admission there was an elevation of the temperature to 103°F. With the use of chemotherapy, this was brought down to normal levels; however, dyspnea increased and the patient expired on the eighth hospital day.

Autopsy findings disclosed both lungs to be voluminous, almost meeting in the midline beneath the sternum. The left lung was bound by old, dense adhesions over the posterior and lateral aspects to the thoracic wall. The right lung was firmly fixed, the adhesions being especially dense over the lower lobe and medial surface. The lung weighed 1,325 Gm. The entire lung was discolored except for a small amount of aerated marginal tissue on the lateral side of the upper lobe. The surface was elevated and nodular, other nodules being palpable within the substance of the organ. Dissection of the bronchial tree showed no evidence of malignancy or obstruction. Cut surface of the lung revealed extensive mottling of the studded surface, these markings being prominent throughout the central portion of the lung and the major portion of the upper lobe. These masses were confluent, presented a granular, carcinomatous-appearing surface and adjacent areas were more discrete but also presented a hard grayish carcinomatous appearance.

The right lung was similar in its upper and middle lobes. These lobes were fused and largely replaced by tissue similar to that found on the opposite side. The lower lobe was small and completely atelectatic. The bronchial tree on this side was free from gross obstruction or malignancy; there was no enlargement or apparent involvement of the mediastinal lymph nodes by this process.

Microscopic examination of the lungs showed

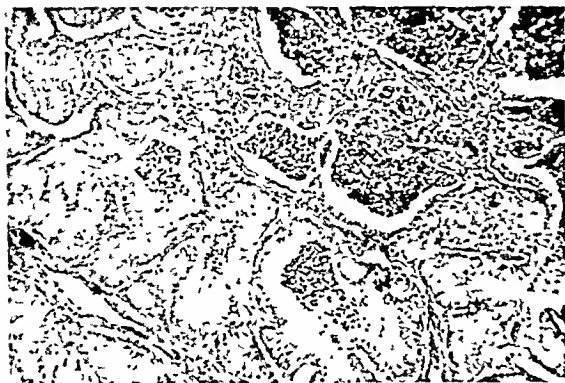


FIG. 1. Case No. 1456. Here can be seen a transition from a flattened alveolar epithelium to cuboidal and columnar mucus-producing glandular epithelium. The septa are thickened and the dilated alveoli are filled with mucopurulent exudate; low power.

a similar picture in each, consisting of a hyperplastic overgrowth of alveolar epithelium with a high columnar type in which the cytoplasm was clear with occasional mucoid, mucus frequently filling the distended alveoli. (Fig. 1.) This process was circumscribed into nodular areas by moderate interstitial fibrosis and in the uninvolved areas there was frequently pneumonic consolidation. There was no evidence of malignancy.

COMMENTS

A brief comparison of several points common to both of these cases may help to emphasize some of the salient features of this disease. Onset was in the latter decades, with cough, dyspnea and production of sputum. Although x-ray films of the chest in each patient pointed to pneumonitis, probably of a granulomatous type, they were not diagnostic. Specific etiologic organisms were not identified. Further routine laboratory procedures failed to be of value and examination of the urine and blood was negative.

The clinical courses were somewhat parallel—a long gradual downhill trend accompanied pulmonary symptoms, with occasional exacerbations. There was even more striking similarity pathologically; in each case there was the massive increase in the size and weight of the lungs. Dense adhesions fixed the lungs to the thorax; there was nodular consolidation throughout

and a variegated, mottled cut surface. Microscopically a particular pattern was observed. In or near the nodular areas was found a net-like arrangement, the stroma of which consisted of normal alveolar septa with variable increase in amounts of supporting tissue. This fibrosis was apparently the result of previous secondary infection and major increases were noticeable in older areas of the disease process as indicated by x-ray findings. The septa were lined by very tall columnar, mucus-producing, non-ciliated cells with oval or round, basal, vesicular nuclei. Larger areas of normal lung tissue were definitely separated from areas previously described by thickened alveolar septa, compressed or atelectatic lung and other areas of minimal alveolar lining hyperplasia and metaplasia. The presence of secondary infection influenced the picture. Grossly it added to the amount of exudate and to the mottled discoloration of the pleural and cut surfaces. The alveoli could be classified or divided according to the type and amount of exudate they contained. Some contained only a few phagocytic cells, others were heavily choked with a mucopurulent exudate while still a third group contained a large number of round phagocytic cells in a background of mucinous material in which no evidence of infection remained. Most of the bronchioles contained large amounts of mucopurulent material. None of these air passages showed any evidence of invasive destruction; most had thickened walls. In a number of sections there was inflammatory loosening and destruction of bronchiolar epithelium.

Only one microscopic difference between these two cases was apparent. In the first case there was a larger proportion of mitotic figures among the hyperplastic alveolar epithelial cells. Whether these represented activity of these epithelial cells themselves or of the reticulo-endothelial phagocytes could not be determined definitely. However, such figures were noted particularly in those cells which had been pushed well into the lumina of the alveoli and many if not all appeared to give rise to the round phagocytic cells

which were extruded well into the lumina of the alveoli after division.

Examination of seventy-six cases of pulmonary diseases from our slide library revealed varying amounts of pulmonary alveolar epithelial hypertrophy and hyperplasia, the lining cells attaining a low columnar pattern in two cases of bronchiectasis. In no cases were tall columnar cells found or any evidence of mucus production. Little or no variation from the normal morphologic pattern was found in the usual case of acute pulmonary disease, for instance in fetal pneumonia, acute passive congestion, acute bronchial and lobar pneumonia and early stages of infarction. Occasional cases of chronic passive congestion showed no change in the areas studied. No change was seen surrounding a Ghon complex and only slight hypertrophy and hyperplasia were noted in four of five patients with lung abscess. In cases of pulmonary tuberculosis much of the increase in size and number of alveolar lining cells appeared to be related to the increased number of alveolar phagocytes, but this was not generally true as numerous phagocytes were found in patients with acute passive congestion, lobar and bronchial pneumonia and lung abscess in which only slight or no hypertrophy or hyperplasia were found. The cuboidal alveolar epithelial cells could be differentiated readily in most cases from the phagocytes and their precursors.

These findings are similar to those of Bell² and others and suggest that a diminution in the oxygen supply to an area of the lung may be the stimulus for hypertrophy and hyperplasia of the alveolar epithelium. However, review of these cases gives no clue as to the pathogenesis of metaplasia to mucus-producing columnar cells.

SUMMARY

Within one year two cases of benign pulmonary adenomatosis were discovered at autopsy. This is a comparatively rare condition, only nineteen human cases having been recorded previously. However, almost all of them had histories and physical and x-ray

findings which were similar. These findings should lead the observer to suspect the condition if they are seen again: (1) There is a long, slowly progressive downhill course, with pulmonary symptoms following an acute infection which never clears completely. (2) There are exacerbations with partial remission of symptoms due to the superimposed infections. (3) X-rays show a diffuse conglomerate pneumonic infiltration, with little change over a period of months or years. (4) To date sputum examinations have revealed no causative organism. (5) Grossly the lungs are voluminous, heavy, with raised, moist, gray patches of tumor. Microscopically there is a transformation of the normal alveolar lining by hyperplasia and metaplasia to a benign mucus-producing columnar epithelium.

Acknowledgment. We wish to express our sincere thanks to Dr. Roswell Schiedt Fidler, Pathologist at The White Cross Hospital, for his helpful advice and criticism.

REFERENCES

1. ALEXANDER, CARTER M. and CHU, Foo. Pulmonary adenomatosis complicated by lobar pneumonia. *Arch. Path.*, 43: 92-101, 1947.
2. BELL, E. T. Hyperplasia of the pulmonary alveolar epithelium in disease. *Am. J. Path.*, 19: 901, 1943.
3. BONNE, C. Morphological resemblance of pulmonary adenomatosis (jaagsiekte) in sheep and certain cases of cancer of the lung in man. *Am. J. Cancer*, 35: 491-501, 1939.
4. BOYD, WM. Surgical Pathology. 5th ed., p. 788. Philadelphia, 1943.
5. COWDRY, E. V. Studies on the etiology of jaagsiekte: primary lesions. *J. Exper. Med.*, 42: 323-333. 1925.
6. COWDRY, E. V. and MARSH, H. Comparative pathology of South African jaagsiekte of sheep and Montana progressive pneumonia of sheep. *J. Exper. Med.*, 45: 571-585, 1927.
7. EWING, J. Neoplastic Diseases. 4th ed., pp. 858-874; 23, 24, 26. Philadelphia, 1940. W. B. Saunders Co.
8. FOOT, N. C. Pathology in Surgery. Pp. 190-191. Philadelphia, 1945. J. B. Lippincott Co.
9. EL GAZAYERLI, M. On the nature of the pulmonary alveolar lining and the origin of the pulmonary alveolar phagocyte. *J. Path. & Bact.*, 43: 357-365, 1936.
10. GEEVER, E. F., NEUBERGER, K. T. and DAVIS, C. L. The pulmonary alveolar lining under various pathologic conditions in man and animals. *Am. J. Path.*, 19: 913-938, 1943.
11. GEEVER, E. F., NEUBERGER, K. T. and DAVIS, C. L. Alveolar cell tumor of the human lung. *Arch. Path.*, 33: 551-569, 1942.

12. GEEVER, E. F., NEUBERGER, K. T. and DAVIS, C. L. *J. Thoracic Surg.*, 10: 557-565, 1941.
13. GEEVER, E. F., CARTER, H. R., NEUBERGER, K. T. and SCHMIDT, E. A. Roentgenologic and pathologic aspects of pulmonary tumors probably alveolar in origin, report of 6 cases. *Radiology*, 44: 319-327, 1945.
14. GRADY, H. G. and STEWART, H. L. Histogenesis of induced pulmonary tumors in strain A mice. *Am. J. Path.*, 16: 417-432, 1940.
15. MACKLIN, C. C. Pulmonic alveolar epithelium. *J. Thoracic Surg.*, 6: 82, 1936.
16. MAXIMOW, A. A. and BLOOM, WM. A Textbook of Histology. 4th ed., pp. 470-481. Philadelphia, 1942. W. B. Saunders Co.
17. MOORE, R. A. A Textbook of Pathology. P. 882. Philadelphia, 1945. W. B. Saunders Co.
18. NEUBERGER, K. T. Primary multiple alveolar cell tumor of human lung. *J. Thoracic Surg.*, 10: 557-565, 1941.
19. NORRIS, ROBERT F. Pulmonary adenomatosis resembling jagziegte in the guinea pig. *Arch. Path.*, 43: 553-558, 1947.
20. PAUL, LESTER, and RITCHIE, GORDON. Pulmonary adenomatosis. *Radiology*, 47: 334-343, 1946.
21. RICHARDSON, G. O. Adenomatosis of the human lung. *J. Path. & Bact.*, 51: 297, 1940.
22. SIMON, MORRIS A. So-called pulmonary adenomatosis and "alveolar cell tumors." Report of a case. *Am. J. Path.*, 23: 413-428, 1947.
23. SIMONDS, J. P. and CURTIS, J. S. Lesions induced in lungs by intravenous injections of tar. *Arch. Path.*, 19: 287-302, 1935.
24. SMIS, J. L. Multiple bilateral pulmonary adenomatosis in man. *Arch. Int. Med.*, 71: 403-409, 1943.
25. STRAUB, M. Microscopical changes in lungs of mice infected with influenza virus. *J. Path. & Bact.*, 45: 75-78, 1937.
26. SWEANY, H. C. So-called alveolar cell cancer of lung. *Arch. Path.*, 19: 203-207, 1935.
27. TAFT, E. B. and NICKERSON, D. A. Pulmonary mucous epithelial hyperplasia (pulmonary adenomatosis). *Am. J. Path.*, 20: 395, 1944.
28. WOMACK, N. A. and GRAHAM, E. A. Mixed tumors of lung: so-called bronchial or pulmonary adenoma. *Arch. Path.*, 26: 165-206, 1938.
29. WOOD, O. A. and PIERSON, P. H. Alveolar adenomatosis in man. *Am. Rev. Tuberc.*, 51: 205-224, 1945.
30. YOUNG, J. S. Epithelial proliferation in the lungs of rabbits brought about by intrapleural injection of solutions of electrolytes. *J. Path. & Bact.*, 33: 363-381, 1930.
31. ZELDES, M. Alveolar lining of the lung in relation to the viability of the fetus. *Arch. Path.*, 29: 748-758, 1940.

Chronic Pulmonary Granulomatosis

Report of Ten Cases

J. M. DENARDI, M.D., H. S. VAN ORDSTRAND, M.D. and M. G. CARMODY, M.D.

Cleveland, Ohio

IN 1943 two of us first reported the occurrence in the United States of an acute pulmonary involvement occurring in workers extracting beryllium oxide.¹ A subsequent, more comprehensive report of acute manifestations in these same patients was published in 1945.² Since the initial publication, beryllium and its compounds have been under investigation as a possible source of both acute and chronic conditions in man although final convincing proof of a relationship is still lacking.

Industrial concerns employing and manufacturing beryllium and its compounds have not waited for conclusive evidence of beryllium toxicity but began at once to develop measures to decrease exposure of their workers to this element. The industry has also taken steps to reduce the amount of beryllium compounds escaping through its various exhausts into the surrounding atmosphere.

The syndrome under discussion is most commonly known as chronic pulmonary granulomatosis. It has been described by Hardy and Tabershaw³ and by Higgins.⁴ It has also been referred to as miliary sarcoidosis, chronic granulomatous pneumonitis, delayed chemical pneumonitis and beryllium sarcoid. The purpose of this report is to make available clinical, laboratory and roentgenographic data to aid in the early diagnosis and management of this chronic pulmonary disease.

It is noteworthy that since 1944 or 1945 exposure to beryllium has been much less frequent because of the steps taken by manufacturing plants. Consequently, in preparing this report we wish to point out that the majority of the case histories presented

in this paper were of those who were exposed to beryllium compounds prior to 1946. Of the many who were exposed before 1946 only a small number have shown any symptoms.

ETIOLOGY AND PATHOLOGY

At present no etiologic factor or combination of factors has been definitely established as the cause of chronic pulmonary granulomatosis. Previously reported cases have been closely associated with the handling of phosphorus in the manufacture of fluorescent lamps.⁵ In the series of cases presented four of the patients worked in a plant producing beryllium and four of the remaining six lived near the plant. However, consideration must also be given to agents other than beryllium such as infection, copper, manganese and zinc. On his last visit to Cleveland, Dr. L. U. Gardner suggested the possibility of a diphtheroid organism or other bacteria or viruses becoming virulent in the presence of certain chemical compounds. In spite of the failure to identify the cause with certainty, public health officials as well as industrial sanitary engineers have drawn attention to beryllium.

Because of lack of knowledge of the exact etiologic factors, little has been advanced theoretically as to the pathogenesis of the disease. On the theory that the etiologic agent is an insoluble organic or inorganic compound it is possible that phagocytes, in the usual response to irritants, engulf the minute particles of the compound in the finer bronchioles and respiratory alveoli. Some of the cells die locally owing to the toxicity of the agent with the characteristic tissue reaction of formation of sarcoid-like

nodules. Other cells are capable of migrating into the local lymphatic system and still others into the blood capillaries, a mechanism which would explain the nodular reaction.

HISTORY

Six of the ten persons reported had not worked with metallic beryllium or its compounds but four of them lived within a radius of 300 meters from a beryllium plant for periods of from one to four years. The fifth lived about three miles from the plant, where her husband was employed, but at no time did she handle his work clothing. Probability of direct exposure was questioned but denied. The sixth patient lived approximately one-half mile from the plant for about one year. She had no complaints nor did she manifest any respiratory difficulty while in this area. Her residence since has been two to three miles from the plant and her only possible contact during this time has been with a friend whose father was employed in a beryllium plant. The entire exhaust material from the plant has not been thoroughly investigated; however, preliminary samples in the proximity revealed minimal contamination with beryllium compounds for a short distance only.

All six of the patients hereby reported as out-plant cases were brunette women who ranged in age between twenty-two and thirty-five years. In five instances the disease had manifested itself from one to eight months postpartum. In the sixth instance the interval between delivery and onset of the disease was almost two years. Of the four remaining patients one worked in a beryllium plant for six weeks during the summer of 1941 and his earliest symptoms appeared while he was in the army in 1944. The second patient was employed in the laboratory of a beryllium plant for twelve weeks from November, 1943 to February 1944, and her first symptoms appeared in August, 1946. Neither had any manifestations of the acute form of the disease while working in the beryllium plant. The third patient worked in a beryllium plant for

eight weeks in 1941. He left this employment after having developed a cough and shortness of breath which he attributed to chemical bronchitis. His first symptoms of chronic pulmonary granulomatosis appeared in January, 1946, and during the intervening years he had not been exposed to any other chemical or occupational hazards.

The fourth patient developed an acute chemical bronchitis in May, 1945. Upon complete recovery two months later he returned to work as a beryl ore grinder. Within ten days he again disclosed clinical symptoms and findings of acute bronchitis. After full recovery he was released from the industry in September, 1945 and has since avoided chemical contact.

Clinical and Roentgenographic Data. The clinical history was characteristic in all cases. The onset was rather insidious and because of the mildness of the process in the early months the patients failed to seek medical attention. The typical history was a mild productive or non-productive morning cough usually following an acute coryza. In a few months the cough became more pronounced and dry in character and sudden changes in air temperature and humidity sometimes elicited a severe attack of paroxysmal coughing. Substernal pain and discomfort were frequently noticed during the coughing attacks or upon attempted deep breathing.

Concomitant with the paroxysmal cough there was exertional dyspnea which became more pronounced as the disease progressed. Acrocyanosis, "watchglass" fingernails and clubbing of the finger tips were present in the later stages.

Physical examination in all patients revealed some weight loss, depending upon the stage of the disease. The vital capacity was diminished greatly, chest expansion was definitely limited and substernal pain was experienced at the height of inspiration. The percussion note was resonant throughout and fine, crackling rales were audible in the hilar areas in the advanced stages of the disease. Abdominal examination proved entirely negative in all except Case 1 during

the terminal months of the illness. No such skin or glandular lesions as were described by Higgins⁴ have been observed.

Laboratory studies, including complete blood counts, Kline and Kahn tests, urinalysis, sedimentation rate, non-protein nitrogen and blood sugar determinations were within normal limits in all cases. Albumin globulin ratio was within normal limits in all cases.

Chest roentgenograms revealing a ground-glass appearance with minute nodules throughout the lungs is one of the outstanding characteristic diagnostic features of the disease. The small nodules are unquestionably the result of coalescing granules. The fact that symptomatic onset of the disease precedes positive roentgenographic findings by several months is verified in the histories of the reported cases. Roentgenograms of the hands in all living patients did not reveal any abnormalities.

Two of these patients died and autopsies were performed. Nodular lesions were confined to the lungs, hilar glands and the liver. The pathologist's reports are given in detail in connection with Cases I and II. Beryllium was not recovered from the tissues of one of the patients in whom an autopsy was performed; in the other quantitative studies were equivocal. Beryllium analysis of the urine revealed small amounts in two patients (Cases VI and VII) and none in the other two patients (Cases III and V).

Differential Diagnosis. There is need for great caution in making a specific roentgenologic diagnosis, especially on single plate observation. All other possibilities must be eliminated by exhaustive exposure investigation, by serial roentgenogram study, by clinical course pattern and by laboratory procedures. Furthermore, the possible co-existence of multiple etiologic factors must be given consideration. Differential diagnosis must include consideration of miliary tuberculosis, tuberculosilicosis, Boeck's sarcoid,^{6,7} miliary carcinomatosis,⁸ pneumoconiosis,^{9,10} erythema nodosum,¹¹ coccidioidomycosis¹² and acute chemical pneumonitis.^{12,13} Differential highlights

have been given by Pascucci¹⁴ in his recent report of similar cases.

Prognosis. The prognosis remains guarded. Most cases have been diagnosed in the later stages of the disease while only a few have been detected in an earlier phase. At the present time the first patient seen in consultation with Dr. L. U. Gardner in 1945 is living and while she has improved clinically, roentgenograms of the lungs remain unchanged. Three others (Cases VI, VII and VIII) have manifested clinical improvement in the last six months and are allowed minimal physical exertion.

Treatment. No specific treatment has been suggested up to the present. Since the cause or causes are not yet established, treatment is empirical. BAL (2,3 dimercaptopropanol) has been used without particular success. Aminophyllin, benadryl and cough sedation have been used symptomatically with some degree of relief. In two patients during attacks of chills, high fever, shortness of breath and severe acrocyanosis intravenous injection of 10 to 50 mg. of benadryl produced an amazing alleviation of symptoms immediately and a sudden drop in the temperature to normal, a condition which persisted for several days.

The most effective treatment at present depends upon early diagnosis and consists of prescribing minimal exertion so that the patient's physical reserve is not impaired. It has been observed that a clear, dry and warm environment is conducive to clinical improvement even though roentgenographic findings remain unchanged. Because of decreased vital capacity in these patients, great caution must be observed to avoid any acute respiratory infection.

CASE REPORTS*

CASE I. A white woman, who was thirty-eight years old at the time of her death on July 15, 1946, complained of a progressive respiratory difficulty of two and one-half years' duration. The apparent onset was in January,

* Clinical data furnished through the courtesy of Dr. M. E. Kishman, Dr. L. Hait, Dr. H. Marsico of Lorain, Ohio, and Dr. Russell Dickason of Vermilion, Ohio.

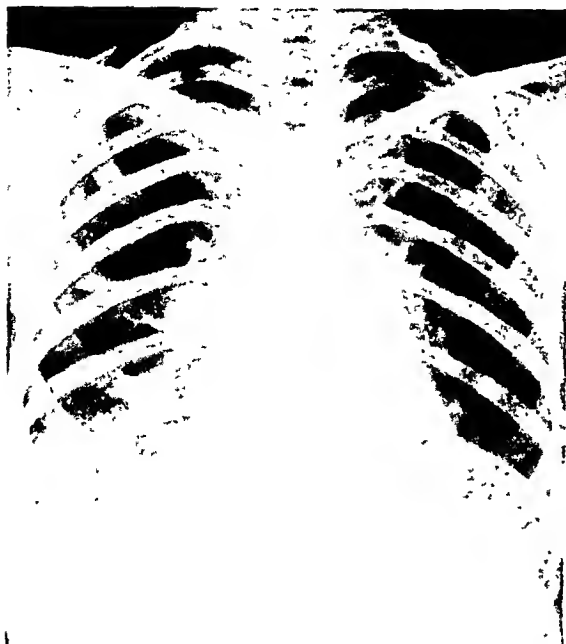


FIG. 1. Case 1. Fine diffuse granular infiltration throughout lung fields, with cardiac silhouette of secondary cor pulmonale; five months prior to death.

1944 when the patient suffered a cold after which she experienced persistent weakness, a slight but constant cough, dyspnea on exertion and a slight loss of weight. She did not have chills or fever. On April 13, 1945, she was delivered of her second child and on October 12th stated that she had lost over 20 pounds during the preceding summer. Her cough had become more pronounced and also spasmodic and while it had been productive during the summer was dry at the time of examination. She complained of severe dyspnea and of substernal pain on inspiration. Examination revealed acrocyanosis and slight clubbing of the fingers and toes. Expansion of the chest was diminished, but percussion and auscultation revealed no abnormality. There was some retraction of the supraclavicular spaces during inspiration. With the patient in the sitting position, distention of the jugular veins was evident almost to the angle of the jaw bilaterally.

Two weeks later the pulse rate was 96. The temperature and blood pressure were normal. Urinalysis, blood count and Kahn and Wassermann tests were also normal. An electrocardiogram showed slight right axis deviation.

Three months later, in February, 1946, the patient's condition had become worse. She complained of a painful, pulling sensation in the mediastinum when in the recumbent position. Severe exertional dyspnea was present.

About five months later and five weeks before her death examination of the chest revealed fine crepitant rales at the bases with sibilant rales over the hilar areas. Chest expansion was limited. Edge of the liver was palpable 2 cm. below the costal margin. There was edema of the ankles and feet. A month later on July 13, 1946, there were signs of early right-sided cardiac failure. The patient died two days later.

During 1944 and until August, 1945 the patient had lived about two blocks from a plant extracting and using beryllium. She then moved approximately one and one-half miles away. She first noticed symptoms on foggy days in January, 1944 when she could smell fumes from the plant. From September, 1944 to April, 1946, some three months preceding her death, five roentgenograms* of the chest were taken, one of which is shown in Figure 1.

An autopsy was performed. The significant observations made on microscopic examination of the lungs by the staff pathologist are as follows:

The alveolar walls were irregularly thickened by infiltration of lymphocytes and focal accumulation of histiocytes and foreign body giant cells. No necrosis was apparent. Occasional small purplish staining (calcified) lamellated bodies, 50-75 micra, were present in infiltrate. In patches small irregular alveoli with cuboidal epithelium enclosed by thickened walls were evident, and other patches of dilated alveoli with partly thin, partly thickened walls. Connective tissue septa were only partly involved by infiltrate; pleura showed a moderate lymphocyte infiltrate and rare histiocyte focus.

One parabronchial lymph node showed frequent, poorly demarcated foci of large mononuclear cells, frequent giant cells of Langhans' type and occasional calcified bodies. A small branch of pulmonary artery revealed marked intimal thickening due principally to connective tissue increase but with small foci and single lipophages. The anatomic diagnosis was chronic granulomatous interstitial pneumonitis and chronic granulomatous lymphadenitis. A typical area of granuloma of the lung is shown in Figure 2.

There was severe parenchymatous degeneration of the liver. Occasional nodules with giant and round cells were found. There were increased numbers of round cells in the portal

* All roentgenograms were read and interpreted by Dr. Delbert Russell, Lorain, Ohio.



FIG. 2. Case I Typical area of pulmonary granulomatosis. A focal accumulation of histiocytes and foreign body giant cells with infiltration of lymphocytes; no apparent necrosis.

tracts. The pathologic diagnosis was chronic granulomatous interstitial pneumonitis.

The results of beryllium determinations performed on lung tissue were as follows: mg. Be/sample—Nil or <0.000015 ; mg. Be/100 Gm.—Nil or <0.00008 ; results of similar determinations on the formalin in which the tissue was sent were as follows: mg. Be/sample—Nil and mg. Be/L.—Nil.

CASE II. A white woman, aged twenty-five at the time of her death February 17, 1948, complained of a mild non-productive cough and steady loss of weight over a period of nearly two years. The loss of weight in the two-year period was 11 pounds. About one and one-half years before she died in June, 1946 she noticed dyspnea on exertion and intermittent fever and arthralgia.

On August 12, 1946, this patient had a pulse rate of 100 with normal temperature and blood pressure. There were a few fine crepitant rales over the lung bases posteriorly but no other physical findings in the chest. Vital capacity was approximately 70 per cent of normal. Urinalysis and blood studies were normal. At this time a roentgenogram of the chest revealed

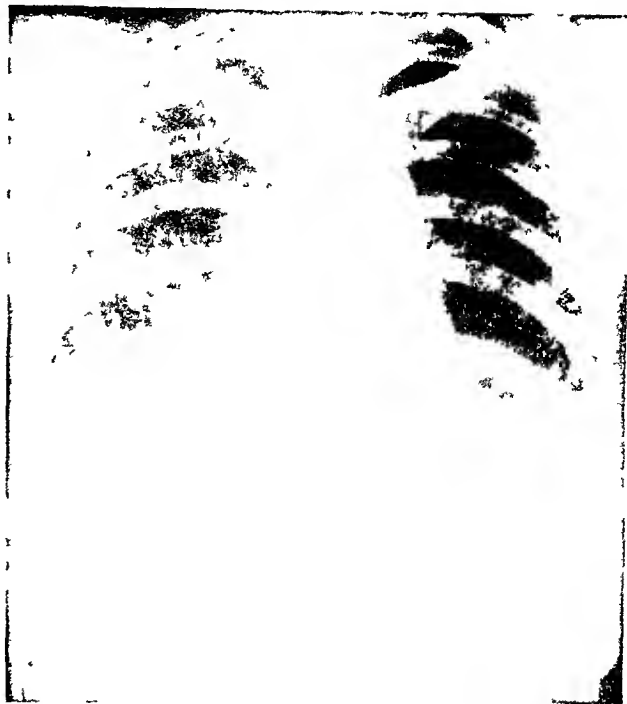


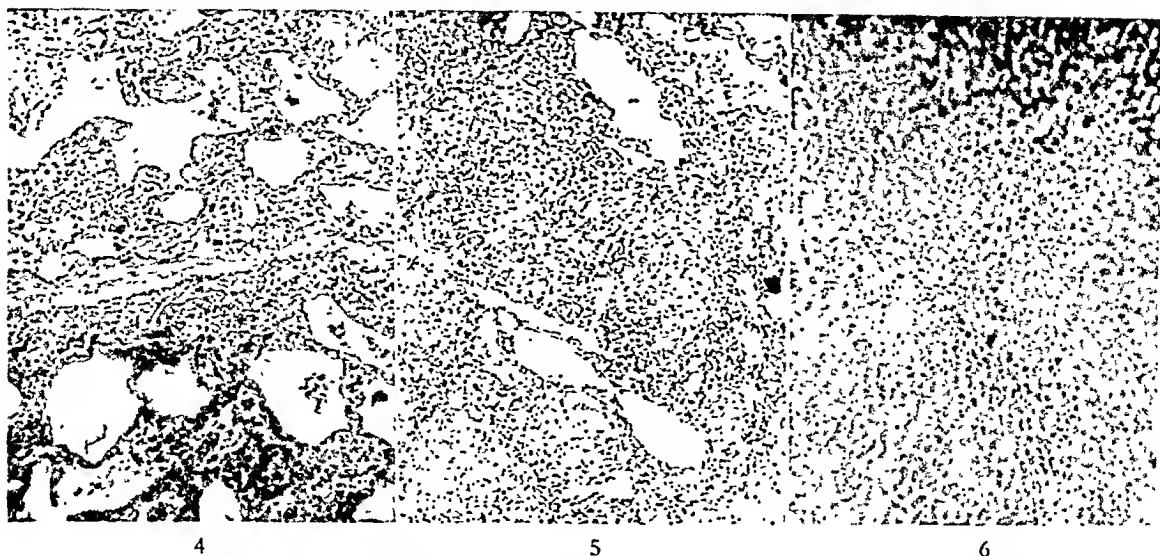
FIG. 3 Case II Minute nodulation throughout all lung areas, five months prior to death.

accentuated hilar shadows especially on the right side with a diffuse, generalized granular appearance of all lobes of the lungs.

By June, 1947, about seven months prior to death, the patient had developed purpuric areas of the skin and mucous membranes. She had suffered from a severe pulmonary hemorrhage. Laboratory studies at this time revealed a deficiency of platelets and secondary anemia; roentgenograms of the chest showed some clearing of the lung field without associated evidence of clinical improvement. An x-ray of September 9, 1947, is shown in Figure 3.

The final roentgenograms in November, 1947 about three months prior to her death revealed a generalized granular infiltration throughout both lungs. Shortly preceding death acrocyanosis became evident, aggravated by slight exertions. Clubbing of the fingers was present. Excursions of the chest were rapid and shallow. Heart rate was 124. Fine and coarse, moist rales were audible throughout both lung fields. Occupational exposure to chemicals could not be determined. During 1941 the patient had lived approximately one-half mile from a beryllium plant. She had two normal pregnancies and deliveries in 1942 and 1944.

An autopsy was performed and the results of the microscopic examination of the tissue was made by the staff pathologist. Focal accumulations of histiocytes of foreign body and Langerhans' type with variable numbers of lympho-



FIGS. 4, 5 and 6. Case II. Figure 4 shows focal accumulations of histiocytes of foreign body and Langhans type in lung. Lymphocytes and plasma cells are frequent in interstitial tissue of alveolar walls. Figure 5 reveals discrete tubercle formation in lymph nodes, with widening of the sinuses; no tubercle bacilli were found. Central necrosis of liver cells is seen in Figure 6.

cytes and plasma cells were found in the lungs principally in the interstitial tissue of the alveolar walls. Fibroblastic proliferation was present, usually focally arranged. However, in a subpleural zone, approximately 0.5 cm. in thickness, there was in addition to the focal lesions a fairly pronounced diffuse increase in thickness of the alveolar walls due to connective tissue proliferation and an infiltration of variable numbers of lymphocytes and plasma cells. The alveolar lumina in this latter zone were of definitely reduced size and contained a few alveolar phagocytes and occasional polymorphonuclear cells. Necrosis was not apparent in the tubercle-like lesion. Tags of loosely arranged fibrous tissue and sometimes diffuse patches of loosely arranged connective tissue were present on the pleural surfaces. A moderate amount of pink-staining granular coagulum was apparent in some alveoli. In certain areas the alveoli were greatly dilated and the atriae of bronchi presented similar dilatation. In one section there were a few small zones of hyaline fibrosis, including brownish-black pigment, with marginal histiocytes. Photomicrograph of lung tissue is seen in Figure 4.

There were many focal accumulations of histiocytes and an occasional giant cell in the lymph nodes. (Fig. 5.) A moderate amount of hyaline fibrosis was present in patches. The tubercles were discrete and showed no tendency to conglomeration; the sinuses were widened. Sinuses were prominent in the spleen but con-

tained only a few red cells. There was an increase of connective tissue of the pulp. In an occasional nodule there was a discrete accumulation of histiocytes with reticulo-endothelial cells and rarely with a giant cell of foreign body type. None of these were apparent in the pulp. An occasional small patch of hyaline fibrosis was detected in the lymph nodules.

Principally in the central areas of the liver, Figure 6, but also to a slight extent in the mid-zonal areas, there were small patches of necrotic liver cells, with a moderate number of polymorphonuclear cells at times in the vicinity of the oxyphilic liver cells.

Pathologic diagnosis was interstitial granulomatous pneumonitis, granulomatous lymphadenitis, chronic passive congestion of the spleen, slight toxic splenitis and moderate focal necrosis of the liver.

CASE III. A twenty-five year old white woman first noticed a dry cough in December, 1944. Dyspnea on exertion did not develop until a year later following the birth of a second child. At this time the patient also had anorexia, some loss of weight and pain in the substernal region which was accentuated by attempted deep inspiration. All of these symptoms became progressively worse.

At the time of examination on February 10, 1948, a small amount of exertion produced dyspnea, acrocyanosis and a disagreeable spasmodic cough productive of mucoid sputum devoid of blood. The "coughing spells" were

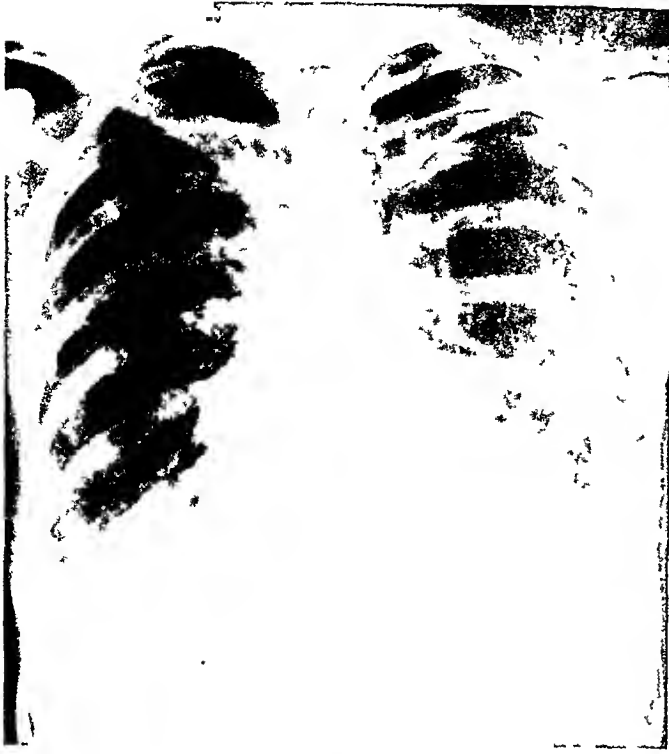


FIG. 7

FIG. 7. Case III. Bilateral pneumothorax complicating diffuse pulmonary granulomatosis.



FIG. 8

FIG. 8. Case VII. Punctate type of granular-appearing infiltration diffusely scattered through both lung fields.

worse in the morning and were aggravated by breathing cold air. The patient was afebrile throughout the illness.

The patient weighed only 85 pounds. Pulse rate was 86 and the blood pressure was 90/65. Vital capacity was one-third of calculated normal and the lungs were resonant to percussion. Expansion of the chest was greatly limited. Fine, moist rales and sibilant rhonchi were audible in both lung fields. There was severe acrocyanosis with clubbing of the fingers. Routine urine and blood studies did not reveal any serious abnormalities either at this time or a month later. Roentgenograms of the chest disclosed a generalized, diffuse, granular, streaky infiltration throughout both lung fields. There was bilateral pneumothorax. (Fig. 7.)

The only possible occupational exposure occurred while the patient worked in a tooth-paste packing room and inhaled a considerable amount of paper dust during the latter months of 1943. Her husband worked in a beryllium plant for about eight weeks after their marriage in December, 1942, but the patient did not handle any of his working clothes nor did any respiratory symptoms develop during this period. Exertional dyspnea became apparent in 1945 immediately after the birth of a second child.

A roentgenogram of this patient's chest on

March 23, 1948, is shown in Figure 7 with bilateral pneumothorax complicating diffuse pulmonary granulomatosis.

CASE IV. A white woman, who was thirty-four years old when first observed in April, 1945, complained of chills, tightness and pressure over the chest, some shortness of breath and palpitation of the heart on slight exertion. She had lost 10 pounds during the preceding eight months. The symptoms had become progressively more severe and included a change in the color of her fingernails. The symptoms were reported to have begun in April, 1942, eight months after a pregnancy which was the patient's fourth.

Physical examination revealed engorgement of the veins of the eyegrounds and cyanosis of the lips. The chest was resonant throughout, but expansion was definitely diminished. Fine, moist rales were heard throughout the lungs, especially over the bases; the edge of the liver was barely palpable. Acrocyanosis and slight deformities of the finger tips were present although urinalysis and routine blood studies revealed no particular abnormalities. A roentgenogram showed a diffuse miliary type of infiltration throughout both lung fields giving a groundglass appearance. The hilar and main bronchial trunks showed increased markings in both lung fields.

During her three week hospitalization she received calcium gluconate intravenously and aminophylline. For two weeks she was given 20,000 units of penicillin every four hours. Slight improvement occurred with some clearing of the apices of the lung, lessened fatigue and shortness of breath on exertion and diminution in the amount of sputum. The patient was somewhat improved six months later but still complained of dyspnea on exertion. Chest examination revealed some limitation of expansion and sibilant rhonchi were heard throughout the hilar areas and bases; vital capacity was 82 per cent of calculated normal. Laboratory studies were essentially within normal limits and roentgenograms of the chest disclosed a diffuse miliary type of infiltration throughout both lung fields. During the eight months preceding her initial examination the patient had been exposed to inhalation of fumes from a beryllium plant located about 100 feet from her residence. She was not, however, employed by the plant or apparently otherwise exposed.

On June 29, 1948, she gave birth to a normal boy following an uneventful pregnancy. When re-examined on October 1, 1948, she stated that she had improved considerably since leaving the neighborhood of the beryllium plant. The vital capacity was increased to 90 per cent of the computed normal and the acrocyanosis and clubbing of the fingers were comparatively less pronounced.

CASE V. A twenty-one year old white woman was first examined in September, 1947, her symptoms dating from about nine months previously when she had developed a spasmodic cough with some production of mucus. Shortly thereafter she noticed some dyspnea on exertion which was aggravated on damp days. Coughing spells were also more acute on damp days and in the mornings. Substernal pain and tightness became apparent, and a month or two before her visit her fingernails turned blue and showed a tendency to curve downward. Chills and fever were also reported.

On the day of admission to the hospital in September, 1947 the patient developed dyspnea with chills and fever. Her temperature was 101°F., pulse 134 and respiration 35. Acrocyanosis with clubbing of the fingers were evident. A persistent cough existed, perspiration was profuse and the patient's breathing was rapid and shallow. Fine and coarse moist rales

were heard over the right lung and sibilant rhonchi over both lungs. Chest expansion was greatly limited. Urinalysis was negative and the blood count was within normal limits except for a leukocytosis of 10,450.

Roentgenograms, Figure 8, revealed a widespread, diffuse, miliary-like, granular-appearing infiltration throughout both lungs. Each granule appeared to be discrete. The patient was given oxygen almost constantly for a week and penicillin for two weeks. Streptomycin was administered for five days. A roentgenogram taken at the time of discharge from the hospital seventeen days after admission did not show any appreciable change.

The patient was re-examined about two months later. Her vital capacity was 86 per cent of calculated normal and the laboratory tests were essentially normal.

This patient for the approximate five years from 1940 to 1945 had lived within one block of a beryllium plant. In November, 1945 she moved about 1 mile away but returned to the earlier address in January, 1947 shortly before the first symptoms became manifest. The same month she gave birth to a son. She was examined on June 29, 1948, and stated that since moving to her new residence three months ago she had noticed a definite improvement. The vital capacity was 90 per cent of normal but physical examination of the chest was the same as on the last examination.

CASE VI. A white woman, twenty-eight years old, first noticed symptoms in December, 1946. These symptoms of weakness and loss of ambition became progressively worse. Approximately five months later in May, 1947 she developed a spasmodic non-productive cough, more pronounced in the mornings on awakening. About one month later the cough became productive with mucus occasionally slightly tinged with blood. The cough grew worse when she inhaled fumes from a beryllium plant near which she lived. Fever and chills at frequent intervals developed in July, 1947. At this time she had a fever of over 101°F. The symptoms of dyspnea were more evident on humid days while the patient had lost 22 pounds between the onset of her symptoms and the time when she was first observed on November 24, 1947. A bluish color of her fingernails was noted during the summer of 1947 as well as downward curving of the fingernails. On May 28, 1948, the patient completed her second pregnancy.

On examination acrocyanosis was noted with slight clubbing of the finger tips. Systolic pressure was 100, pulse rate was 120, the vital capacity was 68 per cent of normal and the chest expansion was definitely diminished. Fine crackling rales and sibilant rhonchi were audible, especially in the hilar and basal areas of the lungs. Resonance of the lungs was normal.

Roentgenograms of the chest revealed a diffuse granular type of infiltration throughout both lung fields. The granular areas were somewhat discrete and generalized haziness was shown throughout both lungs. Examination of the urine and blood did not reveal any serious abnormalities except a white blood cell count of 13,300.

This patient had lived approximately one block from a beryllium plant for the four years preceding her first examination in November, 1947, i.e., over three years before any symptoms became manifest. She was last seen in June 1, 1948, and had improved definitely since leaving the neighborhood of the beryllium plant. However, she still complained of cough and shortness of breath on exertion. Examination of the chest did not reveal anything new. The vital capacity was 68 per cent of computed normal.

CASE VII. A white man aged twenty-seven developed a cough with chills and fever in December, 1944 while he was in the army. Roentgenogram of the chest at that time was negative. The chills, fever and cough persisted with the symptoms most pronounced early in the morning. The cough was non-productive. The patient had lost 8 pounds during the six months prior to December 1, 1947, at which time he complained of weakness and exertional dyspnea with some substernal pain and tightness of the chest on inspiration. The symptoms were more evident on humid days.

On examination there was definite acrocyanosis with slight clubbing of the fingers and toes. Pulse rate was 78. Chest expansion was restricted and the vital capacity was 74 per cent. Sibilant rhonchi were heard intermittently over both lung bases. Roentgenograms of the chest (Fig. 8) showed slight enlargement of the hilar shadows but there was no suggestion of nodulation. A punctate type of granular-appearing infiltration was diffusely scattered through both lung fields. The patient has been under observation since that time and has grown progressively worse. Laboratory tests are essentially normal.

The patient had worked in and around a beryllium plant for six weeks during the summer of 1941. His work consisted principally in the construction and handling of bags of beryllium oxide and what he thought was beryllium sulfate. He cleaned out several sulfate vats. He did not complain of any illness during this period, but dust from the bags irritated his throat and produced a cough. With the exception of these six weeks, he was either working on a railroad or serving in the armed forces until February, 1946. Since that time, he has been employed in a radiator plant where his work consists of the chemical testing of iron for sulfur, silica and carbon. He has worked with calcium carbide frequently.

He was last examined on June 29, 1948, at which time he complained of frequent attacks of hyperpyrexia associated with dyspnea. These attacks had occurred at intervals of from two to three times a week during the previous two months. Examination at that time revealed the same chest findings as on the last visit. The vital capacity was 47 per cent of normal. The weight was 124 pounds and the temperature 98°f.

CASE VIII. A white woman thirty-nine years old began to exhibit symptoms in August, 1946. At that time she developed a cold with a cough which persisted until December 1, 1947, the time of her first examination by us. At first the cough was non-productive but after several months sputum was present in the morning. During inspiration and the coughing attacks she was aware of substernal pain and tightness of the chest. In July, 1947 she experienced dyspnea on exertion which has grown progressively worse. By December, 1947 she was able to do only light housework without discomfort. During the entire illness her appetite was good and she gained 8 pounds from June, 1947 to December, 1947.

Physical examination did not disclose any acrocyanosis or abnormal changes of the fingers. Pulse rate was 76. Expansion of both lungs was adequate and equal. Vital capacity was 95 per cent of computed normal although a few wheezy rales were audible throughout the hilar areas. Routine laboratory tests were essentially normal. Roentgenograms on December 1, 1947, Figure 9, revealed a slight enlargement of the hilar shadows but no nodulation. There was a punctate type of granular-appearing infiltration diffusely scattered through both lung fields.



FIG. 9

FIG. 9. Case VIII. Diffuse granular infiltration of lungs

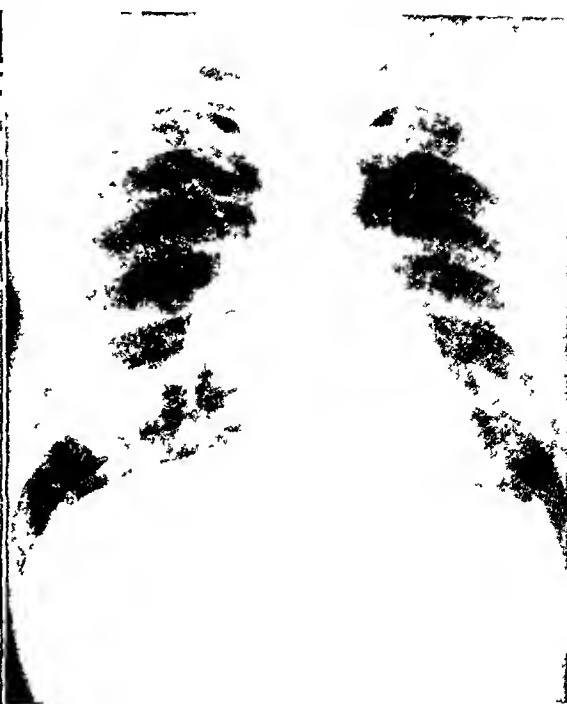


FIG. 10

FIG. 10. Case X. Roentgenogram of chest shows diffuse granular infiltration

This patient was employed in the laboratory of a beryllium plant from November, 1943 to March, 1944. During this period she did not have any respiratory complaints, but because of a papular rash of the hands and forearm was advised to give up her work. For the next three years she resided in northern California and Oregon.

The patient was examined on June 8, 1948, and stated that except for some exertional dyspnea she felt decidedly improved since the last examination. She has not experienced any cough during the last month. Examination of the chest failed to reveal any additional findings since the previous examination. The vital capacity was 77 per cent of normal.

CASE IX. A white man aged twenty-six complained of exertional dyspnea and a persistent cough which had been present from January, 1946 to May 20, 1947. In January, 1946 he had the "flu" with accompanying cough, shortness of breath and arthralgia. The cough was persistent and produced mucoid sputum without blood. He did not have fever. His appetite was poor and he lost 50 pounds in the first twelve months of his illness.

On physical examination his temperature was found to be normal and his pulse rate 98. Chest expansion was diminished and vital

capacity was approximately 50 per cent of normal. The lungs were resonant to percussion but a few fine crepitant rales were heard over both apices and bases. Roentgenogram revealed an extensive generalized granular appearance of all lung lobes. Laboratory studies were essentially normal.

This patient had worked in the fluoride process department of a beryllium plant during the last eight weeks of 1941. His reason for leaving this work was development of cough and shortness of breath. However, he has not experienced chemical or occupational exposure since that time.

His course since October, 1947 does not indicate any clinical improvement although he continued to work contrary to medical advice.

CASE X A white man, forty-eight years old at the time of examination on April 26, 1948, complained of a persistent spasmodic productive cough, anorexia with weight loss and progressive exertional dyspnea beginning in early October, 1947. Since the onset of the illness, he lost over 40 pounds. The coughing attacks have become more frequent and longer in duration and productive of a greenish sputum. Exertional dyspnea became so pronounced that he was forced to give up his work. At present exertional dyspnea is often accom-

panied by vertigo. He has experienced some mild chills and at times stated that he "felt hot."

Physical examination revealed a normal temperature, pulse rate of 75 and respiratory rate of 20. There was no respiratory distress or acrocyanosis and changes of the finger tips. The blood pressure was 96 mm. Hg systolic and 70 mm. Hg diastolic. The vital capacity was 82 per cent of normal and the breath holding test was 20 seconds.

The chest expansion was slightly diminished with the patient's complaint of substernal discomfort at the limit of inspiration. The percussion note was resonant and equal throughout. Breath sounds were of normal character throughout both lungs and no adventitious sounds were audible. Pulmonary roentgenograms showed a diffuse, granular and fibrous-appearing infiltration throughout the parenchyma of both lungs. There was some associated prominence of the hilar shadows but no nodulation at the hila. (Fig. 10.) Laboratory studies of the blood and urine were essentially normal.

The patient was employed in a beryllium plant on April 30, 1945, and first worked for seven days handling beryllium fluoride until transferred to the crystallizing sulfating department for a period of nine days previous to onset of symptoms on May 30, 1945, when he developed exertional dyspnea and a productive spasmodic cough. The clinical and roentgenologic diagnosis at that time was acute chemical bronchitis probably due to beryllium salts. He recovered from this initial attack and returned to work in the same plant on July 9, 1945, in the ore grinding mill. After an additional ten days of work he developed a second attack of acute bronchitis and following complete recovery he was given a medical release from the industry on September 11, 1948, because of his recent illness.

This patient was seen on June 28, 1948, and still complained of a spasmodic cough, shortness of breath and loss of weight. Examination of the chest failed to reveal any changes. The vital capacity was 71 per cent of normal. His weight was 145 pounds.

SUMMARY*

From a review of the pertinent data in ten cases, including two patients who died,

* Since this report was submitted three additional patients have been seen. One patient died and necropsy was performed with findings similar to those previously reported.

it is apparent that a characteristic sequence of clinical symptoms and the typical appearance of roentgenograms permit accurate diagnosis in chronic pulmonary granulomatosis. A history of exposure to certain chemical hazards may aid in the diagnosis, but conclusive evidence of exposure cannot always be secured. Specific treatment is not available. Certain drugs may be used symptomatically with some degree of relief of subjective symptoms. The most effective treatment at present is adequate rest and the avoidance of respiratory infection. All evidence points to early diagnosis as the prime requisite for proper treatment.

REFERENCES

1. VAN ORDSTRAND, H. S., HUGHES, R. and CARMODY, M. G. Chemical pneumonia in workers extracting beryllium oxide; report of 3 cases. *Cleveland Clin. Quart.*, 10: 10-18, 1943.
2. VAN ORDSTRAND, H. S., HUGHES, R., DENARDI, J. M. and CARMODY, M. G. Beryllium poisoning. *J. A. M. A.*, 129: 1084-1090, 1945.
3. HARDY, H. L. and TABERSHAW, I. R. Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds. *J. Indust. Hyg. & Toxicol.*, 28: 197-211, 1946.
4. HIGGINS, H. L. Pulmonary sarcoidosis. *Connecticut M. J.*, 11: 330-339, 1947.
5. KRESS, J. E. and CRISPELL, K. R. Chemical pneumonitis in men working with fluorescent powders containing beryllium. *Guthrie Clin. Bull.*, 13: 91-95, 1944.
6. KING, D. S. Sarcoid disease as revealed in chest roentgenogram. *Am. J. Roentgenol.*, 45: 505-512, 1941.
7. REISNER, D. Boeck's sarcoid and systemic sarcoidosis, (Besnier-Boeck-Schaumann disease; study of 35 cases. *Am. Rev. Tuberc.*, 49: 289-307, 1944.
8. CULVER, G. J. Miliary carcinosis of lungs secondary to primary cancer of gastrointestinal tract. *Am. J. Roentgenol.*, 54: 474-482, 1945.
9. DUNNER, L., HERMON, R. and BAGNALL, D. J. T. Pneumoconiosis in radiator and boiler finishers. *Brit. J. Radiol.*, 18: 377-381, 1945.
10. GARDNER, L. U. Pathology and roentgenographic manifestations of pneumoconiosis. *J. A. M. A.*, 114: 535-545, 1940.
11. KERLEY, P. Significance of radiological manifestations of erythema nodosum. *Brit. J. Radiol.*, 15: 155-165, 1942.
12. CARTER, R. A. Roentgen diagnosis of fungous infections of lungs with special reference to coccidioidomycosis. *Radiology*, 38: 649-659, 1942.
13. CAMIEL, M. R. and BERKAN, H. S. Inhalation pneumonia from nitric fumes. *Radiology*, 42: 175-182, 1944.
14. PASCUCI, L. M. Pulmonary disease in workers exposed to beryllium compounds; its roentgen characteristics. *Radiology*, 50: 23-35, 1948.

Prognosis of Acute Myocardial Infarction*

F. TREMAINE BILLINGS, JR., M.D., BERNARD M. KALSTONE, M.D., JAMES L. SPENCER, M.D.,
CON O. T. BALL and GEORGE R. MENEELY, M.D.

Nashville, Tennessee

CLINICAL expressions of coronary artery disease vary greatly, ranging from immediate death following sudden complete occlusion of a coronary artery to a variety of phenomena resulting from the encroachment upon cardiac reserve and cardiac function of a more gradually reduced blood supply to the myocardium.

This paper records an analysis of 240 cases of acute coronary artery occlusion or acute coronary insufficiency of such degree as to produce myocardial infarction. The purpose of the study is to determine, by a detailed analysis of the hospital records of patients with acute coronary artery occlusion or acute coronary artery insufficiency resulting in infarction, whether any of the data in the clinical history, physical examination or laboratory investigations are consistently useful in predicting the train of events following the acute episode.

In the first part of the report particular note has been made of factors having a bearing on immediate mortality. The term immediate mortality has been arbitrarily used to connote death within thirty days of the acute attack. In the second part advantage has been taken of an unusual opportunity to correlate data acquired from study of the acute heart attack with information concerning patients who were alive after the thirty-day period. One hundred forty-three of the two hundred forty patients whose records were analyzed survived the acute attack. Follow-up data were

obtained concerning all of them and information was available regarding the amount of physical activity in which 120 of these survivors were able to participate.

We recognize the limitations imposed upon this study by the nature of the material. Many patients who develop acute coronary occlusion and myocardial infarcts die immediately before reaching a hospital, others are too sick to be moved, while still others are not considered sick enough to be taken to a hospital.¹

The diagnosis of coronary occlusion with myocardial infarction was listed in 591 clinical records from the wards of the Vanderbilt University Hospital during the years 1925 to 1946 inclusive. Two hundred forty cases satisfying one or more of the following criteria constitute the material for this study: (1) The typical clinical picture of pain not necessarily produced by increased demands on the cardiovascular system nor relieved by nitrites or rest, and usually accompanied by signs of shock, tachycardia, fall in blood pressure, elevation of temperature, leukocytosis and acceleration of the erythrocyte sedimentation rate. (2) Electrocardiographic changes indicative of acute local myocardial damage. (3) The demonstration at autopsy of a recent myocardial infarction with or without a completely occluded coronary artery, or complete occlusion of a coronary artery with or without an acute infarct. Thus there was convincing evidence in each case that a recent acute episode related to coronary

* From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn. This work was supported in part by research grants from the Division of Research Grants and Fellowships of the National Institutes of Health, U. S. Public Health Service, The John B. Howe Medical Research Fund, The Eli Lilly Co., The Ciba Pharmaceutical Products, Inc. and the Research Laboratory of the Thayer Veteran's Administration Hospital.

artery disease had occurred and that serious damage either to the myocardium or to a coronary artery or both was present.

Three hundred fifty-one of the five hundred ninety-one cases were not included because: (1) The criteria necessary for a positive diagnosis were not fulfilled; (2) the hospital admissions were for diagnosis or evaluation of physical status or for rehabilitation some time after an episode of acute coronary disease; (3) a few patients with acute coronary disease died so soon after admission to the hospital that there was no opportunity to obtain data necessary for this study.

The record of only one attack was analyzed in each case. One hundred eighty-four records were of first attacks of myocardial infarction, the remaining fifty-six records were of patients observed during a second or subsequent seizure.

In reviewing the records it was frequently difficult to determine exactly when the acute attack began. Often there was a description of repeated, severe episodes of substernal pain followed within a few hours or days by a more severe but otherwise similar episode accompanied by the symptoms, signs and laboratory findings of myocardial infarction. We believe that these premonitory symptoms were those of coronary artery failure² without permanent damage to cardiac muscle, and that when the blood supply to the myocardium became so deficient as to result in death of muscle the typical picture of myocardial infarction developed.

In the statistical interpretation of the data in this report differences of 2.6 standard deviations or more (a probability of .01 or less) have been considered to be "significant." Differences of more than twice the standard deviation are considered "probably significant." In Tables IV, VI, X and XI the asterisks denote that there is a significantly greater mortality among those cases in which the phenomena so marked are present than among those in which they are absent. Obviously conclusions cannot be

drawn from percentages computed on small numbers.

IMMEDIATE PROGNOSIS OF MYOCARDIAL INFARCTION

Sex and Age Incidence. In the group of 240 patients with acute manifestations of

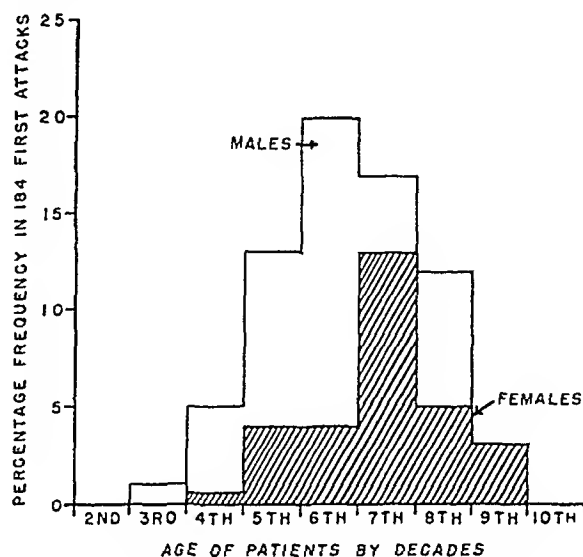


FIG. 1. Frequency distribution by age and sex.

coronary artery disease there were 175 males and 65 females, a ratio of 2.7 to 1. There were ninety-seven deaths within thirty days of the acute episode, or an immediate mortality of 40.4 per cent. Among the 184 patients whose first acute attack was studied the ratio of males to females was 2.3 to 1. Figure 1 demonstrates the frequency distribution by age and sex among these patients. In this group the immediate mortality was 36.4 per cent. As was to be expected the immediate mortality was higher, 53.6 per cent, with the occurrence of a second or third attack. The mortality in the acute stage in other reports in the literature varies from 25 to 45 per cent.³⁻¹¹

Table I is an analysis of the group of 184 patients whose first acute attacks of coronary artery disease were studied with special reference to sex, age and immediate mortality. The mean age at the time of the attack was sixty years, for the males fifty-eight years and for the females sixty-four years. The immediate mortality rate was slightly higher in females than in males.

The relatively larger number of females over fifty years of age was probably a contributing factor. In those persons fifty years or older there were more deaths within thirty days of the acute cardiac episode than among those under fifty. There were

countered angina pectoris in negro males and not at all in negro females. In this study five of seven negro males and two of four negro females gave histories of typical angina pectoris preceding myocardial infarction. The sudden development of con-

TABLE I
FIRST ATTACK: AGE AND SEX INCIDENCE, IMMEDIATE MORTALITY
(DEATHS IN THIRTY DAYS)

Age in Years	Total		Male		Female	
	No. of Patients	Immediate Mortality (per cent)	No. of Patients	Immediate Mortality (per cent)	No. of Patients	Immediate Mortality (per cent)
20-29	2	100	2	100		
30-39	10	20	9	11	1	100
40-49	31	19	23	17	8	25
50-59	44	34	37	38	7	14
60-69	55	38	31	32	24	46
70-79	32	47	22	41	10	60
80+	10	60	5	60	5	60
Total	184	36	129	33	55	44

eleven males with acute coronary artery occlusion under forty years of age and only one female. These data are remarkably similar to those reported by other investigators.³⁻¹¹

Although the percentage of total admissions to Vanderbilt University Hospital of patients with manifestations of acute myocardial infarction increased significantly during the period 1925 through 1946, the per cent of immediate mortality from this disease during the periods 1925 through 1934, and 1935 through 1944, and for the years 1945 and 1946 did not vary significantly.

Racial and Seasonal Incidence. No conclusion regarding racial incidence can be drawn from data presented here because the distribution of patients by race, 229 white and 11 negro patients, was highly selective.

Burch¹² states that he has rarely en-

TABLE II
SEASONAL INCIDENCE AND IMMEDIATE MORTALITY
(DEATHS WITHIN THIRTY DAYS)

Season	Month of Attack	No. of Cases	Per Cent of all Cases	No. of Deaths in Thirty Days	Per Cent Immediate Mortality
Winter	December, January, February	72	30	32	44
Spring	March, April, May	52	22	16	31
Summer	June, July, August	49	20	21	43
Fall	September, October, November	67	28	28	42
Total		240	100	97	40

gestive heart failure or an exacerbation if failure is already present has been cited¹³ as the chief manifestation of myocardial infarction in the negro race. Four of eleven negroes in this group had no congestive failure at any time and three of them had no pain with their attacks. All but two had hypertension. Three of the eleven died within thirty days of their acute attack. No significant difference between negro and white patients with regard to the clinical picture, course, complications, prognosis or immediate mortality was observed.

More persons had attacks in the three coldest months of the year than in the three warmest months. (Table II.) Bean³ and Munck¹⁴ also found a higher incidence during the winter months.

Physical Activity at Onset of Attack. Table III demonstrates that in the majority of cases (64 per cent) the acute episodes of coronary occlusion occurred during complete inactivity. They occurred during mild activity in 14 per cent and during moderate or vigorous activity in 22 per cent of the cases. These findings agree with those of Master and his associates.¹⁵

Symptoms. Not every patient whose myocardium is damaged by sudden interruption of the flow of blood through a coronary

artery experiences symptoms. Death may occur suddenly and under these circumstances the presence or absence of symptoms may not be known. Moreover, Blumgart and Schlesinger¹⁶ have shown that gradual occlusion of a coronary artery with produc-

TABLE III
PHYSICAL ACTIVITY AT ONSET OF ATTACK

Activity	No. of Cases	Per Cent Incidence
Sleeping.....	38	24
Rest in bed.....	44	28
Inactivity (4 hr.).....	19	12
Mild activity.....	22	14
Moderate activity.....	28	18
Vigorous activity-sustained.....	4	3
Vigorous activity-short time.....	1	1
Total.....	156*	100

* Amount of activity not known in other cases.

tion of myocardial fibrosis may occur asymptotically. Nevertheless, sudden interference with the blood supply to the myocardium is commonly associated with a variety of symptoms. A list of these, with the exception of pain, as noted in the 240 hospital records appears in Table iv. The incidence of these symptoms and the associated immediate mortality for each are indicated. The symptom of pain is of such importance that it will be discussed at length.

In considering the prognostic significance of any of these symptoms it is well to remember that the over-all immediate mortality for the entire series of patients studied was 40.4 per cent. It is noteworthy that the existence of any one of three of the symptoms commonly experienced made the prognosis significantly worse. These were dyspnea, cloudy sensorium and clammy sweating. All three are frequently associated with grave dysfunction of the heart, the first with retrograde pulmonary congestion and the latter two with diminished cardiac output. Hiccough was described in only six patients, all males. All terminated fatally.

Pain. Table v shows the distribution of cases and per cent mortality according to location, radiation, type, severity and presence or absence of pain. A number of individuals experienced pain in more than one location with radiation in more than one direction. This is reflected in the table. Usually pain was located in the precordial or substernal regions. Abdominal pain alone was experienced by sixteen patients, ten of whom died within a thirty-day period following the acute attack. There was no statistically significant relationship to the immediate mortality of either location or radiation of pain.

Pain was most frequently described as constricting or crushing in character. No proper evaluation of the severity of a heart attack could be made on the basis of the patient's statement regarding the intensity or character of the pain. An individual with mild pain was just as apt to expire during the acute attack as the patient with severe pain.

Boyd and Werblow¹⁷ observed that pain subsides when congestive cardiac failure develops following acute coronary artery thrombosis and that pain is less likely to be experienced if congestive failure is already present at the time of onset of the symptoms of acute coronary artery occlusion. In the eighty-one patients in this series in whom congestive failure was present at the onset of symptoms of the attack the incidence and severity of pain was as follows: no pain, eleven; mild pain, nine; moderately severe pain, twenty-two; severe pain, twenty-seven; severity unknown, twelve. These figures relating to the occurrence of pain with myocardial infarction in the presence of congestive heart failure differed but little from those for the occurrence of pain in the absence of congestive failure.

Painless Attacks. Considerable controversy has developed in the literature concerning the frequency of painless myocardial infarction. In his review of the subject Kugel¹⁸ found that the incidence varied in the different reports from 0.86 to 75 per cent. One important reason for this dis-

agreement may be the lack of uniform use of the word pain by the patient and the historian. To clarify this point 229 of our cases with adequate records regarding pain were grouped as follows (Table v): (1) Pain was a definite complaint. There were 205

experienced no pain or discomfort was dyspnea.

It has been noted previously that the mortality following silent coronary artery occlusion is high.⁴ In our series the percentage mortality for patients with no pain

TABLE IV
SYMPTOMATOLOGY OF THE ATTACK:
INCIDENCE AND PROGNOSTIC IMPORT

Symptom	Cases with Symptom Present		Cases with Symptom Absent	
	Incidence (per cent)	Immediate Mortality (per cent)	Incidence (per cent)	Immediate Mortality (per cent)
Dyspnea*	71	47	29	20
Restlessness	40	45	60	35
Weakness	38	44	62	36
Nausea	35	38	65	40
Vomiting	33	39	67	40
Sweating, clammy*	28	67	72	29
Cough	28	45	72	32
Cloudy sensorium*	28	65	72	29
Sweating, profuse	26	30	74	43
Vertigo	8	32	92	40
Palpitation	7	32	93	40
Fatigue	7	38	93	40
Stokes-Adams syndrome	5	33	95	40
Hiccough*	2	100	98	37

* Significant.

patients in this group. Seventy-four (36 per cent) died within thirty days. (2) The word pain was not used in the history; nevertheless, a sense of either thoracic oppression, constriction or discomfort was recorded. There were four patients in this group; all survived the thirty-day period following the attack. (3) No pain or discomfort was present. These were genuine examples of "silent" coronary occlusion. There were twenty patients (somewhat less than 10 per cent of the total number) in this group; thirteen (65 per cent) of these patients died within thirty days. A presenting symptom in thirteen of the twenty individuals who

TABLE V
DISTRIBUTION OF CASES AND PER CENT IMMEDIATE MORTALITY ACCORDING TO LOCATION, RADIATION, TYPE, SEVERITY AND PRESENCE OR ABSENCE OF PAIN

Location, Radiation, Type and Severity of Pain	Incidence (per cent)	Mortality (per cent)
Location: substernal or precordial	79	33
epigastric	20	37
abdominal	6	43
interscapular	4	33
arms only	1	67
other	2	20
Radiation: left arm	26	31
both arms	23	32
shoulders	22	24
neck and jaws	8	18
back	6	58
abdomen	4	29
right arm	2	33
other	3	
non-radiating	32	47
Type: constricting or crushing	60	23
sharp or knife like	30	46
dull	23	33
aching	18	29
choking	8	15
burning	7	27
boring	2	
other	4	33
Severity: severe	45	38
moderately severe	34	27
mild	11	38
Total with pain	90	36
Pain denied, chest discomfort present	2	
No pain, no discomfort, "silent"	8	65
Total without pain	10	54

or discomfort was 65 per cent whereas for those who experienced pain it was 36 per cent.

Past History. In a study of coronary artery occlusion the past history would seem to be of particular importance insofar as it is related to the status of the patients' cardiovascular system or to any diseases or

abnormalities which render the patient more susceptible to arterial occlusion and more likely to die as a result of damage to the myocardium should sudden occlusion of a coronary artery occur.

It is noteworthy that the analysis of our records of 240 patients with myocardial

TABLE VI
HISTORY RELATIVE TO STATUS OF PATIENTS'
CARDIOVASCULAR SYSTEM AND ASSOCIATED
DISEASES

History	Cases in which Present		Cases in which Absent	
	Incidence (per cent)	Immediate Mortality (per cent)	Incidence (per cent)	Immediate Mortality (per cent)
Previous heart complaints (excluding dyspnea) . . .	72	42	28	38
Hypertension	54	37	46	41
Angina pectoris	54	40	46	41
Congestive failure*	40	55	60	30
Gallbladder disease (clinical and autopsy findings)	13	52	87	38
Diabetes mellitus†	13	57	87	38

* Significant.

† Probably significant.

infarction revealed that sixty-six patients (28 per cent) gave no history of symptoms specifically referable to the cardiovascular system prior to the acute attack. The immediate mortality among these patients was essentially the same as for the group as a whole. (Table vi.)

1. *Congestive Heart Failure:* A past history of congestive heart failure was obtained in over one-third of the patients in this series (Table vi) and the vast majority of patients with such a history presented signs of congestive heart failure at the onset of the acute episode of coronary artery occlusion. The immediate mortality in this group of patients was 55 per cent in contrast to 30 per cent for the group in which there was no history of cardiac failure preceding the

acute attack of coronary occlusion. This corresponds closely with the observations of others.^{5,11,19,20}

2. *Angina Pectoris:* There was a past history of angina pectoris in approximately one-half of the patients in this series. (Table vi.) However, the immediate mortality for patients with previous angina pectoris was essentially the same as for those who had not had this symptom. Fisher and Zuckerman¹⁹ reported a less favorable prognosis for patients giving a history of angina pectoris whereas Levine and Rosenbaum⁴ believed that angina pectoris in the past improved the outlook of the individual with an acute myocardial infarction. Discussing coronary artery disease in patients under forty years of age, Glendy and associates²¹ reported that a past history of angina pectoris improved the prognosis of occlusion. In our series eight patients under forty years of age had had angina pectoris. Four died within thirty days of the acute episode. The over-all immediate mortality in this age group was 36 per cent.

3. *Hypertension:* All patients with a history of systolic blood pressure greater than 150 mm. Hg or diastolic pressure greater than 100 mm. Hg were considered to have hypertension. According to this classification a little over one-half (54 per cent) of the patients in the series had hypertension. (Table vi.) The incidence of hypertension was significantly higher among the females (69 per cent) than among the males (48 per cent). The immediate mortality following coronary occlusion among all hypertensive patients was essentially the same as among those whose blood pressure had been normal. The incidence of hypertension in studies of acute coronary occlusion or myocardial infarction, as reported in the literature, varies from 41 to 70 per cent.^{4,9,22-25} The opinion that the previous existence of hypertension has no prognostic significance in this condition has been expressed.^{11,19,26} Levine and Rosenbaum,⁴ in their study of 208 cases of myocardial infarction, found the immediate mortality higher among patients with hypertension.

4. *Hypertension and Angina Pectoris*: Seventy-two patients with a history of hypertension also experienced attacks of angina pectoris prior to the acute episode of coronary artery occlusion. It is apparent (Table VII) that neither the presence nor absence of a

TABLE VII
RELATION BETWEEN IMMEDIATE MORTALITY AND A HISTORY
OF HYPERTENSION AND ANGINA PECTORIS

	Incidence (per cent)	Immediate Mortality (per cent)
Neither previous angina pectoris nor hypertension .	22	45
Previous angina pectoris without hypertension .	22	41
Hypertension without previous angina pectoris	24	35
Both previous angina pectoris and hypertension	33	38

history of angina pectoris and hypertension, alone or combined, affected the immediate mortality in our group of patients. Levine and Rosenbaum⁴ found that a history of angina pectoris without hypertension was associated with a more favorable outlook than a history of hypertension in the absence of previous angina pectoris.

Of the women in our series 14 per cent had had neither previous angina pectoris nor hypertension. Eppinger and Levine²⁷ observed that myocardial infarction occurred very rarely in women in the absence of a history of either angina pectoris or hypertension (two of a total of fifty-nine women).

5. *Associated Diseases*: (1) *Diabetes mellitus*—Thirty (13 per cent) of the patients in our series had diabetes mellitus. (Table VI.) The incidence was higher in females, thirteen of sixty-three (21 per cent), than in males, 17 of 174 (10 per cent). Similar observations have been recorded by others.^{3,5,9,10} About one-half (17) of the patients with diabetes mellitus died within thirty days of the acute

heart attack. The presence or absence of previous hypertension was known in all the females with diabetes mellitus and in sixteen of the seventeen males. It is of interest that while only nine of the sixteen males in this group had hypertension, twelve of the thirteen female diabetics had elevated blood pressure.

(2) *Disease of the Gallbladder*—Breyfogle²⁸ and Walsh and his associates²⁹ found a higher incidence of disease of the gallbladder in patients with coronary artery disease than in those with normal or only minimally sclerosed coronary arteries. Pertinent information was available in 228 of the clinical records analyzed by us. (Table VI.) Twenty-nine records (13 per cent) contained either clinical or postmortem evidence of gallbladder disease. To determine the incidence of gallbladder disease in a general group of patients examined at autopsy 231 protocols were reviewed. These were selected so as to correspond with relation to age, race and sex to the records which are the subject of this study. Protocols describing advanced coronary artery disease were excluded. Gallbladder disease was considered to have existed if either stones or cholecystitis were recorded, or if cholecystectomy had been performed during life. The incidence of gallbladder disease in this control group was 22 per cent. The incidence of gallbladder disease in our two series does not confirm the findings of other authors.^{28,29}

(3) *Other Diseases*—Utilizing the aforementioned method of comparison we could establish no correlation between the occurrence of peptic ulcer and coronary artery disease. However, it is of interest and probably significant that eleven (17 per cent) of the sixty-five patients with coronary disease examined at autopsy had gastrointestinal diverticula while they were found in only twelve (5 per cent) of the 231 control patients.

Family History. The family history relating to heart disease was recorded in 192 cases. In 45 per cent of these a family history of heart disease was present. Other studies^{3,25}

reveal a similar incidence of heart disease in the families of cardiac patients. The presence or absence of a family history of heart disease bore no significant relationship to the immediate mortality in our series.

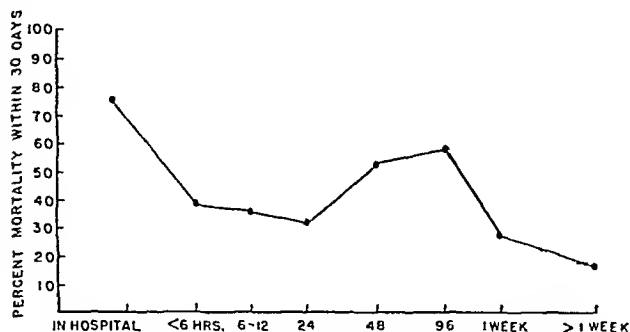


FIG. 2. Mortality in relation to time elapsing between attack and hospitalization.

Habits, Occupation and Habitat. We found it impossible to determine satisfactorily any effect of tobacco, alcohol, coffee or inadequate or irregular meals on prognosis. In general no very convincing relationship between occupation and immediate mortality could be recognized. However, there was higher immediate mortality (54 per cent) among patients living in rural areas than among those living in cities (35 per cent) and among farmers (58 per cent) than among professional men and tradesmen (30 per cent). These differences are statistically significant. They are best explained perhaps by the fact that the percentage of the urban group brought to the hospital within twenty-four hours of the onset of the attack was twice that of the rural patients.

Prognostic Significance of Time Elapsing Between Attack and Hospitalization. From our study early hospitalization following an episode of coronary occlusion seems an important factor favoring survival. This is demonstrated in Figure 2. Forty-two of the patients whose case records were analyzed were already in the hospital when the myocardial infarction occurred. Twenty-three of them were in the hospital for reasons other than heart disease, eight having recently undergone surgical operations. The remaining nineteen were receiving hospital care for some type of heart disease. The immediate mortality among the group in

the hospital at the time of the coronary occlusion was high (74 per cent), probably because the patients comprising this group were already sick and less able to survive the additional cardiac insult.

The patients who were admitted to the

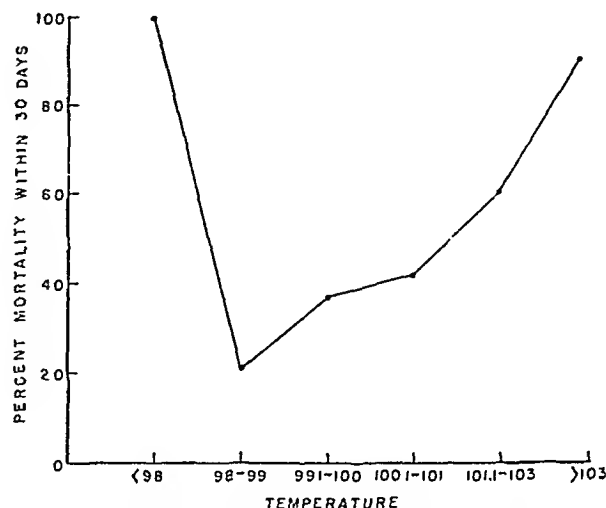


FIG. 3. Temperature with attack and mortality.

hospital within twenty-four hours of the onset of the attack seemed to have a better chance for survival than did those who were admitted between twenty-five and ninety-six hours. This difference is probably significant. Among those admitted ninety-six hours after the attack the immediate mortality was significantly lower, possibly because the most seriously ill patients had already died or because the attack in those who survived to be hospitalized after this length of time was not so severe.

Temperature. The degree of temperature elevation during the attack proved to be a helpful prognostic guide. In those cases in which the temperature during the first week was known it was found that the likelihood of an early death increased directly with the degree of temperature elevation. (Fig. 3.) This is in accordance with other reports.^{4,5,30,31}

There were six patients whose temperature remained subnormal during the entire period of observation. None survived the immediate attack. Four were moribund or in shock when first seen and died within forty-eight hours. The other two died suddenly on the sixteenth and twenty-first days.

Pulse. Most observers are agreed that a rapid pulse rate associated with acute myocardial infarction indicates a poor prognosis.^{4,5,6,32} The prognostic value of a slow pulse with the attack has not been emphasized.

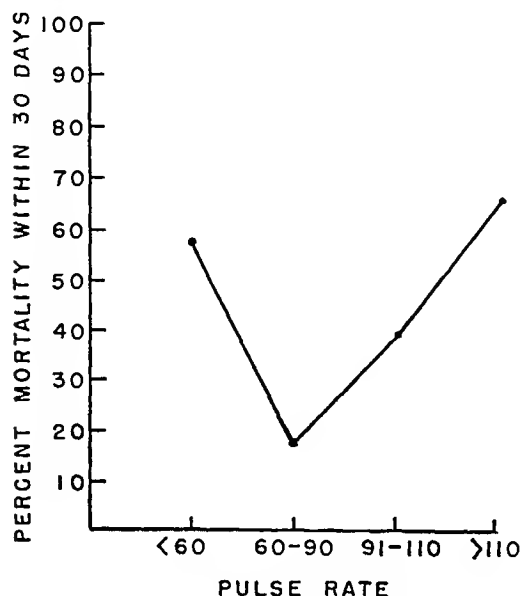


FIG. 4. Pulse rate with attack and mortality.

A pulse rate of more than 90 beats per minute was recorded in over one-half of the patients whose rates shortly after the acute attack were known. In about one-third of the cases the rate was more than 110 beats per minute. The immediate mortality among those whose pulse rate exceeded 110 beats per minute was significantly high. (Fig. 4.) A pulse rate between 60 to 90 beats per minute was associated with low immediate mortality. Bradycardia of less than 60 beats per minute was observed during the first week after the attack in twenty-one patients, over half of whom died within thirty days. Patients with complete auriculoventricular block are not included in this group. It seems that a pulse rate slower than 60 beats per minute or faster than 110 beats per minute during the first few days following the attack is ominous. The three patients with complete auriculoventricular heart block survived the acute episode. Two died within the year of heart disease other than acute infarction. The

other is leading an active life seven years later.

Blood Pressure. A fall in blood pressure is considered to be one of the cardinal features of myocardial infarction. This occurred in approximately one-half of the patients in

TABLE VIII
BLOOD PRESSURE WITHIN TWENTY-FOUR HOURS OF THE
ATTACK DIFFERENCE IN PROGNOSTIC IMPORT BETWEEN
HYPERTENSIVE AND NORMOTENSIVE PATIENTS

Blood Pressure Behavior	Patients with Hypertension		Patients with Normal Blood Pressure	
	Incident (per cent)	Immediate Mortality (per cent)	Incident (per cent)	Immediate Mortality (per cent)
No change	38	31	47	25
Any fall . . .	54	40	43	62*
Less than 50 mm	15	25	36	64*
50 mm. or more	39	46	7	50
Rise . . .	8	12	10	11
Total . . .	100	35	100	40

* Probably significant

our group. In the series as a whole a fall in blood pressure at the onset of the attack was associated with significantly high mortality. However, when hypertension existed prior to the attack the fall in blood pressure appeared to alter the prognosis but little, if at all, whereas any fall in pressure was of grave portent in the previously normotensive group. (Table VIII.)

In seventeen patients a rise in blood pressure with the acute attack was observed; fifteen survived. Levine and Rosenbaum⁴ reported an immediate rise in blood pressure in ten patients, all of whom survived. However, Chambers³³ reported only one survivor in a group of five similar patients. The elevation of blood pressure which occurs occasionally in myocardial infarction has been attributed to the severity of the pain.^{4,6,26} Analysis of the records of the seventeen patients whose blood pressure rose revealed that eight experienced severe,

six moderately severe and one mild pain. One patient experienced no pain during the attack. In one case the record was unsatisfactory for analysis.

Pulse Pressure. A low pulse pressure has been reported by others^{4,26} to be an un-

TABLE IX
RELATIVE IMMEDIATE MORTALITY OF OBESE, NORMAL
AND UNDERWEIGHT PATIENTS

Weight	Incidence (per cent)	Immediate Mortality (per cent)
Obese.....	33	32
Normal.....	51	39
Underweight.....	16	60*

* Probably significant

favorable prognostic sign. In this series there were thirty-five patients whose pulse pressure fell below 25 mm. Hg at some time following their attack and the mortality rate was 77 per cent. The mortality rate for those whose pulse pressure was maintained above this level was 33 per cent.

Weight. The impression has long existed that obese individuals are prone to develop cardiovascular disease.^{39,40} One-third of the 240 patients were described as obese while one-sixth were underweight. The immediate mortality of the obese patients was 32 per cent and for the patients of average weight 39 per cent; it was probably significantly higher (60 per cent) for underweight patients. (Table ix.) Seventy-one per cent of the patients who were overweight had hypertension.

Signs Observed Immediately Following Coronary Artery Occlusion. When associated with myocardial infarction the phenomena listed in Table x are usually expressions of the resultant cardiac dysfunction. Our study reveals that the presence of some of them was of grave prognostic significance.

Heart Sounds. Pericardial friction rub, gallop rhythm, "weak" or "poor quality" of heart sounds and arrhythmias are the auscultatory abnormalities commonly associated with myocardial infarction. The

incidence and attendant mortality of these and certain other abnormalities are shown in Table xi.

The figures for the incidence of the phenomena listed are within the range

TABLE X
SIGNS OBSERVED WITH ACUTE ATTACK OF CORONARY
ARTERY OCCLUSION WITH INCIDENCE AND ASSOCIATED
IMMEDIATE MORTALITY

Signs with Acute Episode	Incidence (per cent)	Mortality (per cent)
Rales*.....	58	52
Hepatomegaly*.....	42	50
Cyanosis*.....	39	61
Ankle edema†.....	29	53
Venous distention.....	21	41
Cheyne-Stokes respiration*.....	16	74
Shock*.....	14	79
Generalized edema*.....	11	74
Ascites†.....	9	64
Jaundice.....	2	40

* Significant

† Probably significant

TABLE XI
MANIFESTATIONS OF CARDIAC ABNORMALITIES: INCIDENCE
AND ASSOCIATED IMMEDIATE MORTALITY

Manifestations of Cardiac Abnormality	Incidence (per cent)	Mortality (per cent)
Weak or poor quality sounds*.....	44	50
Extrasystoles.....	28	47
Markedly enlarged heart*.....	27	55
Gallop rhythm.....	26	39
Pericardial friction rub.....	14	39
Auricular fibrillation*.....	11	65
Pulsus bigeminus.....	4	70
Pulsus alternans.....	3	57
Reduplication of first sound.....	2	20
Thrills.....	2	60
Diastolic murmur, apex.....	2	40
Diastolic murmur, apex and base.....	1	33
Diastolic murmur, base.....	1	
Auricular flutter.....	2	
Pulsus paradoxus.....	2	50

* Significant

established by previous studies.^{4,34} Some authors^{4,5,30} have stated that gallop rhythm implies poor prognosis. Pericardial friction rub,⁴ auricular fibrillation and pulsus alternans³⁰ have also been considered grave

signs. In this series neither gallop rhythm nor friction rub appear to have prognostic significance. Levine and Rosenbaum⁴ found gallop rhythm was of grave import when the infarct was posterior but of no significance in anterior wall infarctions. In the

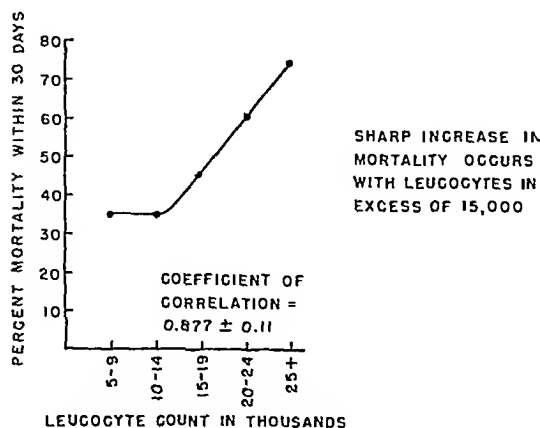


FIG. 5. Leukocytosis and immediate mortality.

study herein reported there was no correlation between gallop rhythm, location of the infarct and mortality. Forty-three of the sixty-one patients in whom gallop rhythm occurred had congestive heart failure. The frequent association of these conditions is well known.³⁵ The immediate mortality associated with auricular fibrillation, poor quality of the heart sounds and marked cardiac enlargement was significantly high.

Laboratory Data. Laboratory data were for the most part not helpful in indicating prognosis. The chief prognostic aid appeared to be the leukocyte count. There was direct relationship between the degree of leukocytosis accompanying the attack and the patient's chance of survival. Marked leukocytosis indicated a poor immediate outlook. (Fig. 5.) This has been consistently observed by others.^{4,5,30} Twelve patients had white blood cell counts of more than 25,000 per cu. mm. Nine died within thirty days. Chambers⁵ reported ten similar cases in which none of the patients survived.

The degree of acceleration of the erythrocyte sedimentation rate was of no prognostic importance. Venous pressure, vital capacity and blood circulation time were not determined in a sufficient number of patients

to make statistical analysis significant. Cholesterol blood levels were determined in sixty-five of the patients. Thirty-five patients had levels between 150 and 250 mg. per cent. Twenty-five survived the acute episode. A cholesterol level of more than 250 mg. per cent was present in twenty-two patients. Twenty survived. Eight patients had levels below 150 mg. per cent. Four of them survived. The immediate mortality for the patients with either high or low cholesterol levels did not differ significantly from the immediate mortality of the patients with levels in the normal range. Anemia did not seem to be an important factor in the etiology of myocardial infarction. There were only six patients with hemoglobin values of less than 10 Gm. per cent.

Location of Myocardial Infarct. The location of the infarct was determined with accuracy in 139 cases, either by autopsy examination or by electrocardiographic tracings. There were eighty-two infarcts of the anterior wall of the heart and fifty-seven infarcts of the posterior wall. There was no significant difference in the immediate mortality in these two groups. In this series the location of the infarct had no relationship to the frequency of various signs and symptoms accompanying the attacks, to the factors in the past history or to the subsequent course. This is of interest in view of the findings of Levine and Rosenbaum⁴ who developed several such relationships. The incidence and mortality figures for our anterior and posterior infarct groups are similar to others in the literature.^{11,14,19,23,37}

Digitalis and Quinidine. One hundred fourteen patients with myocardial infarction received digitalis. It was usually given because of the presence of congestive failure or of cardiac arrhythmias. Forty-nine per cent of these patients died within thirty days of the acute attack. This figure is significantly higher than the figure for patients not receiving digitalis. However, the presence of either congestive failure or auricular fibrillation made the prognosis poor and it seems improbable that digitalis

made it worse. We have insufficient data on the effect of digitalis in the absence of congestive failure or arrhythmias to draw conclusions. Others have found it harmful.^{11,38}

Twenty-four patients in this series received quinidine at the time of the acute attack because of cardiac arrhythmias. Sixteen (67 per cent) expired within thirty days. Seventy-three patients with cardiac arrhythmias were not treated with quinidine. The immediate mortality among patients in these two groups is not significantly different. Quinidine was used in the hope of preventing cardiac arrhythmias in twenty-one patients. Eight of these patients died within thirty days following the acute attack. Thus quinidine, regardless of the reason for its use in this series, did not appear to affect the prognosis either favorably or unfavorably.

PROGNOSIS AFTER SURVIVING THE ACUTE ATTACK

One hundred forty-three of the two hundred forty patients whose records were analyzed in this study survived the acute attack. In 120 cases it was possible to ascertain roughly the amount of physical activity enjoyed by the survivors. Seventy patients were able to return to usual or somewhat reduced physical activity within a few months following the acute episode. In fifty, chronic invalidism ensued with partial or complete confinement to bed. The survival rates for the group as a whole and for the two subgroups are compared with the rate for a Tennessee population of the same age, race and sex distribution. Figure 6 is a graphic demonstration of the survival curves of the four groups of people as determined by the actuarial method. The graph is plotted with a logarithmic vertical scale so that the slope of a line depends on the mortality rate.

Among the 143 patients who survived the acute attack the mortality rate was higher during a three-year period following the acute episode than for the Tennessee population. Thereafter the mortalities followed about the same pattern. The mortality rate

for patients able to resume activity was higher than that of the normal population for the first two years only. The mortality rate for patients completely or partially confined to bed remained significantly high at all times.

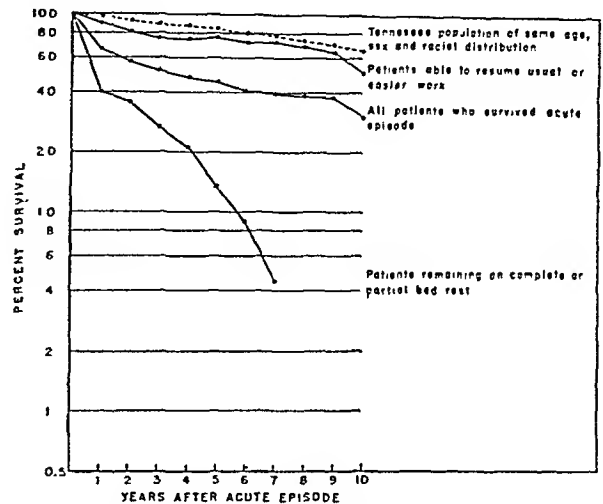


FIG. 6. Myocardial infarction—survival rates; survival curves plotted on a logarithmic scale. The slope of a line segment is a measure of the mortality rate during the period in question. Parallel slopes indicate similar mortality rates. Computed from mortality rates published by U. S. Bureau of the Census.

The ability of patients to return to full or moderate activity following acute heart attacks depends to a large extent on the preservation of adequate cardiac reserve. In addition the patient's general physical condition exclusive of the cardiovascular system must be such as to allow him to be active. We studied the records of the 120 patients whose degree of activity subsequent to the heart attack was known to determine if possible what factor could be shown to be related to a failure to return to work once the acute coronary episode had been survived. Table XII enumerates the conditions which, when present before, during, or after the acute attack, were associated with significant reduction in the patient's chances of resuming activity. It is noteworthy that a history of angina pectoris before the acute attack or its presence afterward was not unfavorable.

COMMENTS

It is obviously important at the time of an acute coronary episode to be able to

determine if possible (1) whether the patient has a good chance of surviving the acute attack and (2) whether having survived the acute episode the condition of the patient's heart will allow for a resumption of some type of activity. The study herein reported

TABLE XII
FACTORS SIGNIFICANTLY UNFAVORABLE TO RETURN
TO WORK

Factor	Per Cent Able to Return to Work	
	with factor present (per cent)	with factor absent (per cent)
Concomitant diseases		
History of rheumatic fever.	17	60
History of peptic ulcer	17	60
Marked arteriosclerosis	44	76
Diabetes mellitus.	38	60
Congestive heart failure		
Whether occurring before, during or after acute episode, particularly as manifested by:		
Dyspnea.	42	82
Cheyne-Stokes respiration		61
Cyanosis..	38	66
Ankle edema	22	70
Ascites...	14	56
Hepatomegaly	26	76
Râles.....	33	78
Venous distension	38	64
Markedly enlarged heart	28	66
Urinary casts....	31	67
Circulatory collapse		
Auricular fibrillation	31	62
Extrasystoles..	43	67
Gallop rhythm	38	66
Miscellaneous		
Systolic murmurs, apex.	35	73
Systolic murmurs, base	29	65
Hospitalization for other purposes		62

was undertaken with the hope of shedding additional light on these questions. We were encouraged in this hope by the fact that there were available records of 240 patients all of whom were carefully studied while under observation in a hospital. The material seemed especially valuable for the purposes of the study because information

regarding the subsequent course of events following discharge from the hospital was available in all the patients (143) who survived the acute attack.

SUMMARY AND CONCLUSIONS

The hospital records of 240 patients with myocardial infarction secondary to either occlusion of a coronary artery or to coronary artery insufficiency were analyzed.

1. Ninety-seven patients (40.4 per cent) died within thirty days following onset of the acute episode.

2. Certain data obtained from the clinical history, physical findings and laboratory investigations were found to be consistently useful in predicting the train of events following development of myocardial infarction:

3. The immediate mortality (thirty days) was high in the presence of any one or more of the following circumstances: (1) A history of congestive heart failure prior to development of the infarct; (2) signs or symptoms of congestive failure or circulatory collapse at the time of the acute attack; (3) absence of pain at the time of the attack; (4) a delay in hospitalization of from more than twenty-four hours to ninety-six hours, inclusively, after the onset of the attack; (5) development of myocardial infarction in a patient already in the hospital; (6) a pulse rate faster than 110 or slower than 60 beats per minute with the attack; (7) a temperature elevation greater than 101° F. or subnormal during the acute attack; (8) cardiac enlargement at the time of the acute attack; (9) presence of auricular fibrillation at the time of the acute attack; (10) leukocytosis in excess of 15,000 with the attack.

4. Follow-up information was obtained concerning the 143 patients who survived the acute attack including data regarding the amount of physical activity engaged in by 120 of these survivors. (1) The following factors were found to influence adversely the likelihood of returning to an active life after surviving an attack of myocardial infarction: occurrence of congestive heart failure either before, during or after the

acute episode; occurrence of circulatory collapse at the time of the acute attack; occurrence of either transient or persistent auricular fibrillation, gallop rhythm or extrasystoles at the time of the acute attack; presence of systolic murmurs at the time of the acute attack; hospitalization for other purposes at the time of the acute attack; a history of either rheumatic fever or peptic ulcer prior to the acute attack and the presence of either advanced arteriosclerosis or diabetes mellitus. (2) The survival rate of those patients who were able to return to some type of useful activity was significantly higher than among those completely or partially confined to bed. This was to be expected when bed rest was mandatory because of diminished cardiac reserve; however, the observation suggests that after a reasonable convalescence, severe restriction of physical activity beyond the requirements imposed by limited cardiac reserve affords little or no protection to the patient who has survived the acute attack.

Acknowledgment: The authors wish to express their appreciation to Dr. Margaret P. Martin, Assistant Professor of Preventive Medicine and Public Health, Vanderbilt University School of Medicine, for her cooperation and guidance in the statistical aspects of this investigation.

REFERENCES

1. WOLFERTH, C. C. Present concepts of acute coronary occlusion. *J. A. M. A.*, 109: 1769, 1937.
2. FREEDBERG, A. S., BLUMGART, H. L., ZOLL, P. M. and SCHLESINGER, M. J. Coronary failure. *J. A. M. A.*, 138: 107, 1948.
3. BEAN, W. B. Anatomy of the heart—a morphological and clinical appraisal of 300 cases. I. Predisposing and precipitating conditions. *Am. Heart J.*, 14: 684, 1937.
4. LEVINE, S. A. and ROSENBAUM, F. F. Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction. *Arch. Int. Med.*, 68: 913, 1215, 1941.
5. CHAMBERS, W. N. Acute myocardial infarction. *New England J. Med.*, 235: 347, 1946.
6. WHITE, P. D. Heart Disease. 3rd ed. New York, 1944. The Macmillan Co.
7. BLAND, E. F. and WHITE, P. D. Coronary thrombosis (with myocardial infarction); ten years later. *J. A. M. A.*, 117: 1171, 1941.
8. BRUENN, H. G., TURNER, K. B. and LEVY, R. L. Notes on cardiac pain and coronary disease. *Am. Heart J.*, 11: 34, 1936.
9. SMITH, C., SAULS, C. and BALLEW, J. Coronary occlusion: a clinical study of 100 patients. *Ann. Int. Med.*, 17: 681, 1942.
10. MASTER, A. M., DACK, S. and JAFFE, H. L. Age, sex, and hypertension in myocardial infarction due to coronary occlusion. *Arch. Int. Med.*, 64: 767, 1939.
11. MINTZ, S. S. and KATZ, L. N. Recent myocardial infarction; an analysis of five hundred and seventy-two cases. *Arch. Int. Med.*, 80: 205, 1947.
12. BURCH, G. E. and VOORHIES, N. W. A study of the incidence of coronary occlusion and angina pectoris in the white and negro races. *Am. J. M. Sc.*, 198: 685, 1939.
13. HUNTER, W. S. Coronary occlusion in negroes. *J. A. M. A.*, 131: 12, 1946.
14. MUNCK, W. The pathological anatomy of sudden heart death. *Acta path. et microbiol. Scandinav.*, 23: 107, 1946.
15. MASTER, A. M., DACK, S. and JAFFE, H. L. Activities associated with the onset of acute coronary artery occlusion. *Am. Heart J.*, 18: 434, 1939.
16. BLUMGART, H. L., SCHLESINGER, M. J. and DAVIS, D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathologic findings, with particular reference to the significance of the collateral circulation. *Am. Heart J.*, 19: 1, 1940.
17. BOYD, L. J. and WERBLOW, S. C. Coronary thrombosis without pain. *Am. J. M. Sc.*, 194: 814, 1937.
18. KUGEL, M. A. The clinical significance of pain in acute coronary occlusion with myocardial infarction. *J. Mt. Sinai Hosp.*, 12: 422, 1945.
19. FISHER, R. L. and ZUCKERMAN, M. Coronary thrombosis. *J. A. M. A.*, 131: 385, 1946.
20. WHITE, P. D. and BLAND, E. F. A further report on prognosis of angina pectoris and of coronary thrombosis. *Am. Heart J.*, 7: 1, 1931.
21. GLENDY, R. E., LEVINE, S. A. and WHITE, P. D. Coronary disease in youth. *J. A. M. A.*, 109: 1775, 1937.
22. PALMER, J. H. The size of the heart after coronary thrombosis. *Canad. M. A. J.*, 36: 387, 1937.
23. NAY, R. M. and BARNES, A. R. Incidence of embolic or thrombotic processes during the immediate convalescence from acute myocardial infarction. *Am. Heart J.*, 30: 65, 1945.
24. GORHAM, L. W. and MARTIN, S. J. Coronary occlusion with and without pain. *Arch. Int. Med.*, 62: 821, 1938.
25. CASSIDY, MAURICE. Coronary disease. *Lancet*, 2: 587, 1946.
26. MASTER, A. M., JAFFE, H. L., DACK, S. and SILVER, N. The course of the blood pressure before, during and after coronary occlusion. *Am. Heart J.*, 26: 92, 1943.
27. EPPINGER, E. C. and LEVINE, S. A. Angina pectoris: some clinical considerations with special reference to prognosis. *Arch. Int. Med.*, 53: 120, 1934.
28. BREYFOGLE, H. S. Frequency of coexisting gallbladder and coronary artery disease. *J. A. M. A.*, 114: 1434, 1940.
29. WALSH, B. J., BLAND, E. F., TAQUINI, A. C. and WHITE, P. D. The association of gall bladder disease and of peptic ulcer with coronary disease: a post-mortem study. *Am. Heart J.*, 21: 689, 1941.
30. KING, H. C. Prognosis in coronary heart disease and after coronary occlusion. *Ohio State M. J.*, 33: 524, 1937.

31. SHILLITO, F. H., CHAMBERLAIN, F. L. and LEVY, R. L. Cardiac infarction. *J. A. M. A.*, 118: 779, 1942.
32. MASTER, A. M., DACK, S. and JAFFE, H. L. Coronary thrombosis: an investigation of heart failure and other factors in its course and prognosis. *Am. Heart J.*, 13: 330, 1937.
33. CHAMBERS, W. N. Blood pressure studies in 100 cases of coronary occlusion with myocardial infarction. *Am. J. M. Sc.*, 213: 40, 1947.
34. WHITE, P. D. and BLAND, E. F. A further report on the prognosis of angina pectoris and of coronary thrombosis. *Am. Heart J.*, 7: 1, 1931.
35. MASTER, A. M. and FRIEDMAN, R. A phonocardiographic study of the heart sounds in acute coronary occlusion. *Am. Heart J.*, 24: 196, 1942.
36. RAVIN, A. and GEEVER, E. F. Coronary arteriosclerosis, coronary anastomoses and myocardial infarction. *Arch. Int. Med.*, 78: 125, 1946.
37. WILLIUS, F. A. Life expectancy in coronary thrombosis. *J. A. M. A.*, 106: 1890, 1936.
38. JENSEN, J. Coronary occlusion. *J. Missouri M. A.*, 34: 77, 1937.
39. WILENS, S. L. Bearing of general nutritional state on atherosclerosis. *Arch. Int. Med.*, 79: 129, 1947.
40. LEVY, R. L., WHITE, P. D., STROUD, W. D. and HILLMAN, C. C. Overweight: its prognostic significance in relation to hypertension and cardiovascular-renal diseases. *J. A. M. A.*, 131: 951, 1946.

Recent Advances in Streptomycin Therapy*

RALPH TOMPSETT, M.D. and WALSH McDERMOTT, M.D.

New York, New York

DURING the few years in which streptomycin has been in clinical usage it has become established as a potent antimicrobial agent of value in the treatment of a large number of infections. Within a relatively short time subsequent to its introduction a large body of information was accumulated in the various clinical studies which fairly well delineated the usefulness of this drug. In the same and correlated studies the important disadvantages attendant upon the use of streptomycin were defined. The advances in our knowledge which have been made since these early studies have not only added extensive confirmation of the earlier findings but have also provided a considerable amount of additional information of value to the clinician. The recent advances have been made along three general lines: (1) the pharmacodynamics of streptomycin in man; (2) studies of a derivative, dihydrostreptomycin, which appears to have certain advantages over the parent compound and (3) further definition of the therapeutic uses of the drug, notably in chronic infections, with surgical procedures or with another antimicrobial agent.

The uses of streptomycin have also been modified to some extent by the introduction of new drugs, chiefly aureomycin and chloramphenicol. It is apparent that these drugs will to some extent replace streptomycin, in that they are active in a number of infections for which streptomycin has previously been the drug of choice. Moreover, they are distinctly preferable from the standpoints of toxicity and the emergence of resistant bacteria during therapy. In some instances it is not yet possible to assess the

relative potency of the newer drugs in comparison with streptomycin and opinions at present may require modification in the light of further experience.

It is the purpose of this review to summarize briefly some of the recent advances in the therapeutic use of streptomycin along the lines mentioned above, and to indicate wherever possible the infections for which the newer drugs appear to be preferable.

PHARMACODYNAMICS

The development of chemical methods of the measurement of streptomycin in body fluids^{1,2} has led to re-evaluation of some of the pharmacodynamics of the drug in humans. The findings have been in general agreement with the investigations previously reported in which biologic assay methods were utilized.^{3,4} The data obtained by the use of the chemical methods, however, not only provide an interesting comparison of methods but also are of sufficient accuracy to permit more detailed analysis than has heretofore been possible. Moreover, they serve to emphasize certain important aspects of the pharmacology of streptomycin which have been recognized previously but which have not appeared to receive adequate consideration in the clinical use of this drug. It seems of interest, therefore, to summarize the main features of the absorption, distribution and excretion of streptomycin as found in these recent studies.¹

Following a single intramuscular injection of streptomycin in man, the drug is rapidly absorbed and the plasma concentrations reach a peak within an hour. Absorption is sufficiently rapid so that at one hour the plasma concentration may be expected to

*From the Department of Medicine of the New York Hospital-Cornell University Medical College, New York, N.Y.

be approximately the same whether the dose has been given intramuscularly or intravenously. The drug is distributed in a percentage of the body weight which approximates that of the extracellular water. With usual doses the values obtained in the blood of humans after a single intramuscular injection of streptomycin are directly related to the dose per unit body weight. In 4.0 to 20 mg. per Kg. doses the rate of fall in serum concentration is proportional to the concentration of the drug in the blood. It is worthy of note that this rate actually is not rapid; and within certain limits, approximately two and one-half to three hours are required for the concentration to fall from any given value to half that value. Excretion of streptomycin is for the most part by way of the kidney. The renal clearance of streptomycin is approximately the same as the glomerular clearance when suitable correction is made for the degree of binding by plasma proteins.⁵

These observations have certain practical implications with regard to the mode of administration of streptomycin. It would appear that little is to be gained by frequent injections of streptomycin as judged by the length of time any given concentration is maintained. Intervals of at least six or eight hours between doses seem permissible, and longer intervals will probably prove generally satisfactory.⁶ The recent experiences in the treatment of tuberculosis with single daily doses of streptomycin and with intervals as long as three days between doses lends support to this belief.^{7,8} Moreover, as the individual dose is increased, there is a proportional increase in the height of the concentrations attained. A number of experimental observations point to the desirability of obtaining relatively high concentrations in the body. Among these are the fact that the rate of killing of bacteria *in vitro* steadily increases as the concentration of the drug is increased.⁹ Another factor to be considered is the recognized occurrence of marked variation in susceptibility of bacteria to streptomycin not only

among the various members of one species, but also among the individual members of a single infecting strain.

NEUROTOXICITY

Although some of the foregoing must remain speculative, it has been obvious from the beginning that an important limiting factor in the widespread use of streptomycin is its neurotoxicity. The occurrence of vestibular dysfunction during streptomycin therapy has been a frequent and distressing problem. There is now ample evidence that these neurotoxic reactions occur in a progressively smaller proportion of cases as the daily dose is decreased. While the administration of 3.0 Gm. of streptomycin daily results in vestibular dysfunction in virtually all adults by the end of three weeks of treatment, doses of 1.0 Gm. daily cause this reaction in only approximately 10 to 15 per cent of patients even though given over much longer periods. It is in this lower range of dosage that it seems possible to effect a significant reduction in the incidence of neurotoxicity by administration of streptomycin on the basis of the patient's body weight. In one small series of patients receiving 1.0 Gm. per day¹⁰ the largest patient was actually receiving 13 mg. per Kg. per day while the smallest was receiving 26 mg. per Kg. per day. No neurotoxic manifestations were observed in those patients receiving less than 20 mg. per Kg. per day. This value which was noted in a small series cannot be broadly applied, but the observations serve to emphasize the fact that failure to consider the patient's weight when administering streptomycin may subject him to unnecessary hazard of loss of vestibular function as well as other toxic reactions.

DIHYDROSTREPTOMYCIN

A recent development of considerable interest has been the reports of clinical trials of dihydrostreptomycin, and in particular the studies of its toxicity. This compound is prepared by the catalytic hydrogenation of streptomycin with reduction of the free

aldehyde group to the corresponding alcohol. Dihydrostreptomycin was first studied in the laboratory as early as 1946^{11,12} and was then found to have essentially the same antibacterial activity *in vitro* and the same acute toxicity for mice as the parent compound. It thus appeared to offer no obvious advantages over streptomycin and was not investigated further at that time. The first clinical trials of dihydrostreptomycin were made in a small number of patients who developed hypersensitivity to streptomycin and in whom it was found possible to continue therapy without interruption by the use of the dihydro derivative.¹⁰ Subsequently, the drug has been prepared in large amounts for clinical trials which have been in progress since early 1947.^{13,14} There is as yet only limited information on the therapeutic effectiveness of dihydrostreptomycin in comparison with streptomycin. From the information available, it appears that dihydrostreptomycin will prove as effective as the parent compound in the same infections and with the same dosage. The derivative possesses no advantage over streptomycin in the problem of the emergence of drug-resistant bacteria during therapy. Micro-organisms resistant to one drug have been found to have a comparable degree of resistance to the other, and there appears to be no difference in the rate at which resistant strains appear during therapy with one or the other drug. The chief interest in dihydrostreptomycin then is in relation to its toxicity.

In general, it may be said that dihydrostreptomycin is qualitatively the same as streptomycin except for its antigenicity, and quantitatively very similar except for its neurotoxicity. The latter difference appears to be sufficiently great; so that if it is confirmed in more extensive studies, it should be a decisive factor in choosing between these two drugs.

The neurotoxic reactions caused by dihydrostreptomycin, both vestibular and auditory, appear to be very similar in character, if not identical, with those caused by the parent compound. It has been the

impression of many investigators that the peculiar type of "dizziness" which characterizes the vestibular dysfunction has not been as severe when produced by dihydrostreptomycin, but such observations are difficult to evaluate. Nevertheless, it has been found that dihydrostreptomycin is less toxic than streptomycin for the vestibular apparatus as judged by the dosage required to provoke the reaction both in experimental animals and man. Doses of 60 mg. per Kg. per day or approximately 3.0 Gm. daily in an adult of average size have caused few reactions during the first four weeks of administration; but when the drug is administered for longer periods, the incidence of vestibular damage is increased appreciably. Daily doses of 40 mg. per Kg. or approximately 2.0 Gm. daily in adults have resulted in neurotoxic manifestations only occasionally over periods as long as six to eight weeks. Comparison of these figures with the toxicity of streptomycin clearly indicates that the dihydro derivative has a lower toxicity for the vestibular apparatus.

Whether an appreciable incidence of vestibular dysfunction will occur with doses of 20 mg. per Kg. per day cannot be stated because of the small numbers of patients thus far treated with this dose. From the results with the larger doses, however, one might anticipate that the occurrence of vestibular dysfunction would be rare.

It has been the general experience that nerve-deafness from dihydrostreptomycin toxicity has been no more frequent than that observed with streptomycin and perhaps has been less frequent. In most clinics the occurrence of any significant loss of hearing has not been encountered even with the prolonged administration of 3.0 Gm. of dihydrostreptomycin daily. In some of these patients, however, there has been a 10 to 15 per cent loss of hearing involving the highest tones, and detectable only by audiometric examination. In a recent survey¹⁵ of approximately 250 collected cases (exclusive of two of the three series described below) in which dihydrostreptomycin was administered for one to three months in

doses which ranged from 1 to 3 Gm. daily, there were no instances of hearing loss sufficient to interfere with the patient's hearing normal conversational tones.

In general, the neurotoxicity produced by dihydrostreptomycin also bears a quantitative relationship to dosage. In the original studies of the toxicity of dihydrostreptomycin, however, it was noted and emphasized that both vestibular dysfunction or deafness might first appear at an appreciable interval after the cessation of the chemotherapy. Such instances of the delayed appearance of neurotoxicity have been infrequent and have occurred after the use of *unusually high doses in the presence of renal insufficiency*.

Nevertheless, three localized outbreaks of neurotoxicity have been encountered with the use of dihydrostreptomycin and it is possible that they may reflect some more serious disadvantage than is now generally believed. The first of these incidents occurred on our own service shortly after the completion of initial studies of dihydrostreptomycin, and after more than one and one-half years of its use here. During the course of a forty-eight hour period five patients who were receiving dihydrostreptomycin in doses of 3.0 Gm. daily suddenly developed severe symptoms of vestibular dysfunction. It would have been unusual in our experience for symptoms of this severity to occur at all in patients receiving dihydrostreptomycin. It was even more unusual that this particular two-day period represented the fourth and fifth days of treatment in one patient, the last of the fourth week in another and periods intermediate in duration in the other three. Thus it appeared that whatever the toxic substance might be, it was probably even more damaging to the vestibular apparatus than streptomycin itself. Every effort was made to determine the cause of this but thus far no definite cause has been ascertained. One factor has been suspected of playing a part, however, and deserves mention although its importance is unknown. It had been the practice to prepare the solutions of dihydro-

streptomycin in the pharmacy and send them to the ward for use. Although stamped with an expiration date, it was possible because of a particularly abundant supply at the time as well as some overstocking on the ward that the particular lot of the drug then in use may have been in solution for an unduly long time. Although this procedure was never actually incriminated, the practice was discontinued and no further difficulty of this sort has been encountered in a subsequent period of nine months. Thus although at present this remains an isolated episode, the possibility still exists that dihydrostreptomycin has the potentiality of causing an explosive type of vestibular toxicity in exceptional circumstances.

Moreover, two groups of investigators^{16,17} working independently have recently observed the phenomenon of the delayed appearance of deafness following the use of only moderate doses of dihydrostreptomycin. It is not yet established whether the disturbingly higher incidence of the reaction localized to these two clinics is merely a reflection of chance distribution or whether it is possible that certain preparations of dihydrostreptomycin might be more neurotoxic than others. Pending more information, about all that can be said is that dihydrostreptomycin is definitely less neurotoxic than streptomycin, but that the dihydro derivative is by no means devoid of neurotoxicity and its behavior in this respect may be less predictable.

Finally, dihydrostreptomycin has proved to be useful in small numbers of patients who have developed some of the manifestations of hypersensitivity to streptomycin. A small proportion (estimated to be 3 to 5 per cent) of patients who have received streptomycin for several weeks have developed drug fever, asthma or other manifestations of hypersensitivity of sufficient severity to warrant interruption of therapy. In the few instances in which it has been tried, it has been possible to continue the antimicrobial therapy of patients experiencing such reactions by the substitution of dihydrostreptomycin.

In summary, it appears that dihydrostreptomycin has a lesser toxicity than streptomycin for the vestibular apparatus; and if it can be established with certainty that the derivative is the equivalent of streptomycin therapeutically, the difference in toxicity may prove decisive in a choice between the two drugs. The three sharply localized outbreaks of neurotoxicity which have occurred with dihydrostreptomycin are disquieting, and their relationship to the intrinsic toxicity of dihydrostreptomycin itself should be established as quickly as possible. The other toxic reactions to dihydrostreptomycin have been no greater than those caused by streptomycin and the derivative has proved valuable in preventing the interruption of therapy in patients who develop manifestations of hypersensitivity to streptomycin.

THERAPEUTIC USES OF STREPTOMYCIN

The scope of the clinical usefulness of streptomycin was well delineated in the first two years of its use, and the various infections for which it has been proved of value are thoroughly reviewed elsewhere. It is worthy of mention that the first definitive report of the efficacy of streptomycin in plague has appeared within the past two years.¹⁸ More extensive experience in the treatment of *Salmonella* infections has strengthened the earlier impression that it has little or no value in these infections. Somewhat to the contrary has been the development of the present opinion in relation to treatment of infections caused by *Ps. pyocyaneus* and *B. proteus*. There is a prevalent belief based on some of the earlier reports that streptomycin is of little or no value in these infections which arise most commonly in the urinary tract. Nevertheless, a review of the reported cases leads to the conclusion that streptomycin has an impressive effect in a large number of the cases of urinary tract infections caused by these two species. Moreover, in a number of these cases the urinary tract infection was accompanied by bacteremia. In Keefer and Hewitt's monograph¹⁹ nineteen cases of

Ps. aeruginosa bacteremia treated with streptomycin are reported. There were nine recoveries and ten deaths. In this same report are included sixteen patients with bacteremia caused by *B. proteus* who received treatment with streptomycin. Twelve of the sixteen were permanently improved by the therapy and there were four deaths. These results, while far from ideal, serve to emphasize the fact that streptomycin may actually prove highly beneficial in infections of this type which are so refractory to treatment with most of the other antimicrobial agents.

CONCURRENT ADMINISTRATION OF STREPTOMYCIN AND ANOTHER ANTIMICROBIAL DRUG

There is at present an increasing interest in the use of streptomycin administered concurrently with another antimicrobial agent appropriate for the particular infection to be treated. In theory, the effects of such "combined therapy" might be detectable in one of two ways. First, the emergence to predominance of drug-resistant microorganisms might be delayed, and second, the course of the infection might be altered to an extent not observed from the use of streptomycin alone. Either type of result would reflect the simultaneous activity of both antimicrobial drugs.

The demonstration that "combined therapy" exerts a greater effect upon the clinical course of an infection than either drug alone can be made satisfactorily only in relatively "drug-resistant" infections. The favorable results noted by Spink and his associates²⁰ from the combined use of streptomycin and sulfadiazine in the treatment of brucellosis are an example of this type of demonstration. It should be noted, however, that although this procedure represents a valuable advance in therapy, it has now been largely superseded by the use of aureomycin or chloramphenicol.

A second example of the concurrent administration of two drugs has been the use of streptomycin and penicillin in the treatment of subacute bacterial endocarditis caused by enterococci.^{21,22} Within the past

two and a half years the writers have employed this therapy in eight patients with this form of endocarditis which has previously been unusually refractory to attempts at treatment. From the results obtained in this small group of cases there can be little question that the concurrent administration of penicillin and streptomycin provides highly effective therapy. Moreover, the results are obtained without the necessity for using massive doses of penicillin or other measures to attain very high concentrations of penicillin in the body. It cannot be stated with certainty whether the effects observed resulted entirely from the streptomycin, inasmuch as the value of streptomycin alone has not been thoroughly established. From the limited information available, however, it seems likely that the concurrent use of the two drugs is more efficacious than either alone.

Another possible indication for the concurrent administration of streptomycin and penicillin is in the treatment of staphylococcal infections. The diseases caused by these species represent virtually the only situation in which the emergence of penicillin-resistant bacteria might constitute a problem. As a consequence, it is advisable at present to attempt to avoid this threat by the simultaneous administration of two antimicrobial agents.

Combined therapy has been utilized also in a small number of patients with tuberculosis in an attempt to prevent or postpone the emergence of significant numbers of streptomycin-resistant tubercle bacilli. In this infection the consequences of the appearance of resistant organisms are magnified because of the chronic nature of the disease process. To effect even a relatively short delay in the emergence of resistance would therefore be highly desirable. Combined therapy in tuberculosis has been studied both with para-amino-salicylic acid and with one of the sulfones administered at the same time as streptomycin. From studies in the Veterans' Administration it appears that the administration of various sulfones, such as promizole, in conjunction

with streptomycin is without influence on the emergence of streptomycin-resistant tubercle bacilli. In contrast, on the basis of preliminary observations by D'Esopo²³ and Karlson²⁴ and their respective associates, it appears that para-amino-salicylic acid administered along with streptomycin may significantly postpone but does not completely prevent the phenomenon of drug-resistance.

STREPTOMYCIN IN TUBERCULOSIS

It was apparent when streptomycin was first introduced into clinical practice that the greatest field of usefulness for the drug would be in the treatment of tuberculosis. This is particularly the case at present because aureomycin and chloramphenicol are preferable drugs for the treatment of many of the gram-negative bacillary infections which were previously best treated with streptomycin. It has been thoroughly established that streptomycin exerts an impressive effect upon the course of tuberculosis in humans and the changes observed in the various forms of the disease during the first few months of streptomycin therapy are now thoroughly familiar. There is very little information available, however, concerning the late results of therapy when streptomycin has been used in quantity for a sufficient period. Accordingly, brief mention will be made of the late results in the New York Hospital-Cornell study which is now finishing its fourth year.

Miliary and Meningeal Tuberculosis. Since January, 1946, twenty-four patients with either acute generalized hematogenous tuberculosis (i.e., miliary), tuberculous meningitis or both forms of the disease have been treated with streptomycin. Ten patients had hematogenous tuberculosis without the complication of meningitis. Relapse occurred in four of these patients. In one instance the micro-organisms were still sensitive to streptomycin and retreatment was successful. Thus seven of the ten patients with only miliary tuberculosis are alive and only three have died. One of these deaths occurred on the sixteenth day in a patient who had far

advanced pulmonary tuberculosis. The period of observation following the cessation of therapy in this group ranged between fifteen and thirty-six months. The important feature is, however, that all seven patients who were well one year after the completion of therapy for miliary tuberculosis were also well thereafter. In other words, no late relapses were encountered and it appears that recovery from miliary tuberculosis is indeed possible.

A second group of five patients had meningitis which was not associated with hematogenous tuberculosis. In two of the five instances meningitis apparently arose from a focus in the vertebral column. Of these five patients, two are alive and three are dead. The two living patients have survived eighteen and twenty-seven months, respectively, following the cessation of streptomycin therapy.

Ten patients, a number equal to the number with hematogenous disease without meningeal complications, also had meningitis. Thus approximately one-half the patients with generalized hematogenous tuberculosis had meningeal involvement as a complication of their illness at some time during its course. This value is lower than in the Veterans' Administration series, in which approximately two-thirds of the patients with miliary tuberculosis developed meningitis at some time during the course of the infection.²⁵ In the present series the combined miliary-meningeal type of infection was fatal to all ten patients. Although the numbers are small, the difference between the outcome in this group and the seven of ten recoveries in the group with uncomplicated miliary tuberculosis is striking indeed. It should be noted that in several instances of the combined disease the deaths were apparently not a direct result of the meningitis but were a consequence of the emergence of drug-resistant miliary infections. Nevertheless, our complete helplessness when faced with the combined infection is apparent.

It is of interest in this connection that in the writers' experience the results attained

from the antimicrobial therapy of pneumococcal meningitis are vastly different when the meningitis arises apparently as a blood-borne infection in association with pneumococcal pneumonia, than when the meningitis arises as a direct extension from a focus in the sinuses or ears.

The type of pneumococcal meningitis which occurs in association with pneumonia is roughly comparable to tuberculous meningitis complicating miliary tuberculosis, and the pneumococcal meningitis which arises from the paranasal sinus or ear is not unlike the tuberculous meningitis which arises from tuberculosis of a vertebra. The case fatality rate of pneumococcal meningitis which arises in association with pneumonia is extremely high, whereas the meningitis without pneumonia is usually controlled by appropriate therapy. The reason for this difference in prognosis is by no means clear, nor is there any particular reason why similar factors should operate with pneumococcal as with tuberculous infections. It is of considerable interest, however, that the results parallel each other so strikingly in these two infections, both of which are rarely fatal when they involve the lung and so frequently fatal when they involve the central nervous system.

Thus of a total of twenty-four patients with miliary or meningeal tuberculosis, fifteen are dead and nine are alive one to three years after the cessation of antimicrobial therapy. It is probable that the complete remission of illness will be maintained in the nine living patients, for late relapses have not been observed in uncomplicated miliary tuberculosis, and the only two living patients who had meningitis have now survived for a minimum period of two years after completion of therapy. It should be emphasized, however, that all but two of the nine survivors are from the group with miliary tuberculosis who were fortunate enough not to develop meningeal involvement. As at least one-half to two-thirds of the patients with miliary tuberculosis do develop meningeal involvement, it is obvious that the survivors of this total group

of infections represent a highly selected group. If the late follow-up results from the Veterans' Administration series parallel the results from the present series, it could be predicted that out of every 100 patients with miliary tuberculosis, approximately thirty will survive. The great majority of these thirty will be those fortunate individuals in whom meningeal complications do not occur.

Pulmonary Tuberculosis. In the late follow-up of the series of pulmonary cases it is of interest to note the number of patients in whom streptomycin therapy was definitive in the sense that no subsequent collapse therapy was necessary. From one standpoint such a value has little meaning unless it is carefully related to the type of pulmonary lesion for which the antimicrobial therapy was used. It is well recognized, for example, that regardless of the extent of the involvement the number of patients requiring collapse therapy would be appreciably smaller in the presence of predominantly exudative lesions without much necrosis than would be the case with subacute or chronic lesions with large areas of destruction. From a broader standpoint, however, the late over-all results are of significance in that they serve to indicate what is to be expected from the use of streptomycin in those types of pulmonary tuberculosis with which the physician is actually confronted.

During the twenty-three-month period from January, 1946, to November 30, 1947, sixty-seven patients with pulmonary tuberculosis received streptomycin therapy. In general, no patient received chemotherapy if it were anticipated that the pulmonary lesions would regress on bed rest alone. Moreover, collapse therapy was never initiated until it seemed evident that no further improvement from the antimicrobial therapy was to be expected.

One and one-half to three years after these sixty-seven patients had completed streptomycin therapy thirteen were dead, thirty-two were alive and well, twenty were alive but still had active pulmonary tuberculosis and two were lost from observation. In seventeen of the thirty-two patients who

had recovered, the only antituberculous therapies used were streptomycin and bed rest. In the other fifteen patients who had recovered it had been necessary to institute collapse therapy subsequent to the administration of the streptomycin. Collapse therapy had also been used in eight of the twenty surviving patients whose tuberculosis has persisted in an active state.

Thus in seventeen of the sixty-seven patients with severe or moderately severe pulmonary tuberculosis, streptomycin (and bed rest) had apparently constituted definitive therapy.

The fact that it was necessary to supplement streptomycin therapy with collapse therapy in the other fifteen successfully treated patients does not mean that streptomycin therapy necessarily failed to exert an impressive control of those infections. On the contrary, in many instances in the present series such collapse therapy would never have been possible were it not for the artificial checking of the infection provided by the antimicrobial therapy. As a consequence, it is to be anticipated that more patients will receive collapse therapy rather than fewer as a consequence of the streptomycin therapy. Moreover, as it is now no longer necessary from an experimental standpoint to observe patients for as long as is possible after drug therapy before the institution of collapse, it may be possible to shorten the period of total therapy considerably by the institution of collapse soon after the start of the antimicrobial therapy. Such a practice is becoming increasingly widespread at present, and within a year or two it should be possible to evaluate its benefits with some degree of precision.

EMERGENCE TO PREDOMINANCE OF STREPTOMYCIN-RESISTANT TUBERCLE BACILLI

The relatively long-term results presented above represent what can be accomplished when streptomycin, despite its handicaps, is incorporated into the over-all treatment of tuberculosis. It is well recognized that the principal handicap consists of the fact that

drug-resistant micro-organisms will emerge and become predominant whenever streptomycin therapy is continued for a sufficient period in the presence of unhealed lesions.

The fact that unhealed or persistently active lesions are a necessary factor for drug resistance is not always appreciated. Many internists not directly concerned with the chemotherapy of tuberculosis have gained the impression that regardless of the status of the lesion all the tubercle bacilli within the patient become resistant to the drug when it has been administered for a certain period. Assuming that the genetic explanation of the origin of drug-resistant infections is correct,^{26,27} and the available evidence appears to point in this direction, if an infection were receding under drug therapy so that a large number of the bacterial population were being sterilized, it would not be anticipated that the emergence of drug-resistant bacteria would occur in a sufficient number to enable them to become predominant. Consequently, in lesions which are rapidly regressing to the point of arrest, it might be anticipated that the micro-organisms remaining therein would be predominantly sensitive and that a relapse of the lesion many months later should be susceptible to retreatment with streptomycin. From the scattered observations which have been made, such would indeed seem to be the case. Conversely, if a lesion remains active throughout a sufficiently long period of drug therapy, sufficient generations of tubercle bacilli would be constantly occurring so that the possibilities of the emergence to predominance of drug-resistant variants would be very real indeed. It is for this reason that the emergence to predominance of drug-resistant strains of tubercle bacilli is much more of a problem in the treatment of patients with cavities than in the treatment of patients with diffuse nodular lesions.^{28,29} It is only when the latter are large or present in great numbers, as in certain cases of miliary tuberculosis, that drug-resistance becomes a problem. Thus, it is presumably not the morphologic arrangement of the lesion in the form of the cavity, but merely the fact

that the cavity happens to represent one of the most frequent forms of persistently unhealed lesions that is responsible for the high incidence of drug-resistance in association with cavities.

Effect of Dose on Emergence of Drug-Resistant Tubercle Bacilli. The attempts to prevent or postpone the emergence to predominance of streptomycin-resistant bacteria by the concurrent administration of another drug have already been discussed. Another approach of substantial but limited promise consists in suitable alterations in the time-dose relationships of the streptomycin dosage regimen. This question is intimately interwoven with the question of the *size* of the daily dose of streptomycin which will produce the maximal attainable antimicrobial effect per unit of time.

The 1 Gm. daily dose of streptomycin is virtually free of serious neurotoxicity and undoubtedly produces significant therapeutic effects in all diseases caused by streptomycin-sensitive species of bacteria. It is by no means established, however, that the effects observed on this low dosage represent the maximal attainable effects.

Because of the many familiar variables it is extremely difficult to measure degrees of therapeutic effectiveness from comparison of the clinical courses of patients treated with various quantities of an antimicrobial drug. This difficulty is particularly accentuated in chronic infections such as tuberculosis in which the principal measurement of continued activity consists of the relatively insensitive tool of serial roentgenographic examinations. One reasonably precise type of observation which may be used in such evaluation of proper dosage, however, is an analysis of the pattern of the emergence of drug-resistant strains of micro-organisms in patients treated on various regimens of the drug.

Bacteriologic studies of this type were conducted by the writers in sixty-four patients with pulmonary tuberculosis who were treated on one or the other of two streptomycin regimens. Thirty-three of the patients received 3 Gm. of streptomycin daily and the remaining thirty-one received

1 Gm. of the drug each day. All strains of tubercle bacilli isolated from both groups of patients before treatment were quite sensitive to streptomycin *in vitro*. Moreover, on both the 3.0 Gm. and the 1.0 Gm. regimens highly resistant strains (i.e., not inhibited by 100 micrograms of streptomycin per cc. of medium) appeared during the treatment in approximately the same incidence. The significant difference between the two treatment groups lay entirely in the incidence of strains with an intermediate degree of drug-resistant (i.e., resistant to concentration which ranged between 2 to 100 micrograms of drug per cc. of medium).

On 1 Gm. of streptomycin daily these "intermediate strains" appeared early and their incidence steadily increased. In contrast, on 3 Gm. daily virtually all strains of tubercle bacilli discharged by the patients were either highly resistant or quite sensitive to streptomycin throughout the observation period. In effect the "intermediate" strains observed on the low dosage regimen represented large numbers of tubercle bacilli which could be killed by the administration of 3.0 Gm. of streptomycin but were not killed on the 1 Gm. regimen.

The following interpretation has been made of these observations. The precise degree of drug-resistance which must be attained by the major part of a bacterial population within the body before essentially complete nullification of streptomycin occurs is not known. Nevertheless, when one bacterial cell with increased resistance to streptomycin is born, the effectiveness of the streptomycin therapy of that infection has been compromised by that little bit. When the survival of bacteria of an intermediate degree of resistance is prevented, the curve of antimicrobial activity would persist at a high level until sufficient time had elapsed for the relatively few highly resistant bacteria to multiply to predominance. From clinical experience this period is approximately ninety days. Thus, the curve of drug effectiveness on the high dosage would be high for several months and then fall off relatively sharply. In con-

trast, when the survival of bacteria of an intermediate degree of drug-resistance is favored, as is the case on 1 Gm. daily, the curve of drug activity would represent more of a slanting diagonal with a steady fall off in activity from week to week. Moreover, the start of the decline in activity would occur soon after the start of streptomycin therapy. It is most unlikely that such a gradual falling off of the effectiveness of streptomycin in pulmonary tuberculosis could be detected by the relatively crude clinical and roentgenologic means currently available.

On the basis of this interpretation of the bacteriologic observations it would seem advisable to adopt one of two alternatives in the streptomycin treatment of each patient with a chronic infection such as tuberculosis. In instances in which the disease constitutes a clear and present danger such as miliary tuberculosis, extensive pneumonias and the like, a large daily dose of streptomycin or dihydrostreptomycin should be used for a period of three or four months. In this situation the eventual nullification of drug activity and some incidence of neurotoxicity would simply be accepted as inevitable.

In those other forms of tuberculosis in which the prognosis without antimicrobial therapy is reasonably good, streptomycin should be used only as an occasional adjunct to the powerful defense mechanisms of the patient by administering the drug once, or at the most twice, each week. In this way some admittedly limited therapeutic benefits can be obtained without continuously providing an environment which favors the survival of tubercle bacilli of intermediate degrees of drug-resistance.

SUMMARY

The recent advances in the use of streptomycin have included: additional studies on its pharmacodynamics in man; further exploration of the relative therapeutic effectiveness of various dosage regimens; and investigations of the value of the concurrent administration of streptomycin with another antimicrobial agent. The neuro-

toxicity of streptomycin and the frequency with which drug-resistant micro-organisms emerge to predominance during therapy continue to be major problems. Relatively small daily doses of streptomycin (20 mg. per Kg.) appropriately adjusted to the patient's weight exert definite therapeutic effects without undue risk of neurotoxicity. It remains to be established, however, that such low doses produce the maximal attainable antimicrobial effect per unit of time. Dihydrostreptomycin is less neurotoxic than the parent compound, but such neurotoxicity as it does produce is less readily predictable. Nevertheless, the dihydro derivative would seem to be preferable at the present time, particularly when relatively intensive therapy is necessary. Encouraging preliminary results have been attained following attempts to prevent or postpone the emergence to predominance of drug-resistant micro-organisms by the use of large daily doses of streptomycin and by the concurrent administration of para-amino-salicylic acid.

REFERENCES

- BOXER, G. E. and JELINEK, V. C. Chemical method for determinations of streptomycin in blood and spinal fluid. *J. Biol. Chem.*, 170: 491, 1947.
- MARSHALL, E. K., JR., BLANCHARD, K. C. and BUHLE, E. L. Colorimetric method for determinations of streptomycin. *J. Pharmacol. & Exper. Therap.*, 90: 367, 1947.
- MARSHALL, E. K., JR. The absorption, distribution and excretion of streptomycin. *J. Pharmacol. & Exper. Therap.*, 92: 43, 1948.
- BOXER, G. E., JELINEK, V. C., TOMPSETT, R., DuBois, R. and EDISON, A. O. Streptomycin in the blood: chemical determinations after single and repeated intramuscular injections. *J. Pharmacol. & Exper. Therap.*, 92: 3, 1948.
- BOXER, G. E., JELINEK, V. C. and EDISON, A. O. Binding of streptomycin to plasma proteins. (Abstract) *Federation Proceedings*, 8: 276, 1949.
- ZUBROD, C. G. Relation of dosage schedule to therapeutic efficacy of streptomycin in the treatment of *K. pneumoniae* infections in mice. *Bull. Johns Hopkins Hosp.*, 82: 357, 1948.
- DEYKE, V. F., FISHER, M. W., JAMES, L. A. and SIDES, L. J. Intermittent dosage schedules of streptomycin with resultant prolonged sensitivity of *M. tuberculosis*. *Ann. Int. Med.*, 30: 619, 1949.
- Veterans' Administration. Minutes of Sixth Streptomycin Conference, p. 199, October, 1948.
- BERKMAN, S., HENRY, R. J. and HOUSEWRIGHT, R. D. Studies on streptomycin. I. Factors influencing the activity of streptomycin. *J. Bact.*, 53: 567, 1947.
- TOMPSETT, R. Relation of dosage to streptomycin toxicity. *Ann. Otol., Rhin. & Laryng.*, 57: 181, 1948.
- BARTZ, Q. R., CONTROULIS, J., CROOKS, H. M., JR. and REBSTOCK, M. C. Dihydrostreptomycin. *J. Am. Chem. Soc.*, 68: 1390, 1946.
- DONOVICK, R. and RAKE, G. Studies on some biological aspects of dihydrostreptomycin. *J. Bact.*, 53: 205, 1947.
- HOBSON, L. B., TOMPSETT, R., MUSCHENHEIM, C. and McDERMOTT, W. A laboratory and clinical investigation of dihydrostreptomycin. *Am. Rev. Tuberc.*, 57: 501, 1948.
- HINSHAW, C., FELDMAN, W. H., CARR, D. T. and BROWN, H. A. The clinical administration of dihydrostreptomycin in tuberculosis. A preliminary report. *Am. Rev. Tuberc.*, 58: 525, 1948.
- MANN, C. H. Personal communication.
- ROMANSKY, M. J. Follow-up data on patients treated with dihydrostreptomycin. Minutes of the Seventh Streptomycin Conference, Veterans' Administration, 1949 (in press).
- ALLISON, S. T., VOLK, R. and VITAGLIANO, G. R. Dihydro-streptomycin in the treatment of pulmonary tuberculosis. *New England J. Med.*, 241: 52, 1949.
- HADDAD, C. and VALERO, A. Streptomycin in bubonic plague. *Brit. M. J.*, 1: 1026, 1948.
- KEEFER, C. S. and HEWITT, W. L. The Therapeutic Value of Streptomycin. Ann. Arbor, Mich., 1948. J. W. Edwards.
- SPINK, W. W., HALL, W. H., SHAFFER, J. M. and BRANDS, A. I. Human brucellosis: its specific treatment with combination of streptomycin and sulfadiazine. *J. A. M. A.*, 136: 382, 1948.
- HUNTER, T. H. Treatment of subacute bacterial endocarditis with antibiotics. *Am. J. Med.*, 1: 83, 1946.
- ROBBINS, W. C. and TOMPSETT, R. The summation of penicillin and streptomycin activity *in vitro* and in the treatment of subacute bacterial endocarditis. *J. Clin. Investigation*, (in press).
- D'ESOP, N. Personal communication.
- KARLSON, A. G., PFUETZE, K. H., CARR, D. T., FELDMAN, W. H. and HINSHAW, H. C. The effect of combined therapy (streptomycin, para-amino-salicylic acid, and promin) on the emergence of streptomycin-resistant strains of tubercle bacilli. A preliminary report. *Proc. Staff Meet. Mayo Clin.*, 24: 85, 1949.
- BUNN, P. A. One hundred cases of miliary and meningeal tuberculosis treated with streptomycin. *Am. J. M. Sc.*, 216: 3, 1948.
- DEMEREK, M. Origin of bacterial resistance to antibiotics. *J. Bact.*, 56: 63, 1948.
- ALEXANDER, H. E. and LEIDY, G. Mode of action of streptomycin on type b *H. influenzae*; origin of resistant organisms. *J. Exper. Med.*, 85: 329, 1947.
- HOWARD, W. L., MARESH, F., MUELLER, E. E., YANNITELLI, S. A. and WOODRUFF, C. E. The role of pulmonary cavitation in the development of bacterial resistance to streptomycin. *Am. Rev. Tuberc.*, 59: 391, 1949.
- HOWLETT, K. S., O'CONNOR, J. B., SADUSK, J. F., JR., SWIFT, W. E., JR. and BEARDSLEY, F. A. Sensitivity of tubercle bacilli to streptomycin: the influence of various factors upon the emergence of resistant strains. *Am. Rev. Tuberc.*, 59: 402, 1949.

Acute Diffuse Glomerulonephritis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. STANLEY E. BRADLEY: The clinical pattern of glomerulonephritis and its association with renal pathology was first pointed out by Richard Bright in 1827. Bright recognized that frequently the disease began acutely with hematuria, albuminuria, edema and a "full and hard" pulse, following scarlatina, exposure or intemperate living. He realized that healing often occurred spontaneously and that apparent subsidence might be followed after a long period by reappearance of edema, albuminuria and marked debility leading inevitably to death. The course of glomerulonephritis and the various forms of renal disease in which anasarca and proteinuria occur have since been more accurately defined but Bright's description of the clinical events stands unchallenged. Studies of the microscopic anatomy of the kidney have been successful in showing the site of the lesion in acute nephritis and in marking out the changes that ensue as the disorder becomes chronically active. Unfortunately, little progress has been made in finding specific therapeutic measures to prevent or halt this process.

During the past twenty years important advances in bacteriologic, biochemical and physiologic technics have opened up new approaches to the problems of etiology and mechanism of symptoms. A rational basis for the treatment of the various manifestations of the disease has been achieved by a better understanding of the functional derangements and it is hoped that specific therapy will ultimately arise from the clarification of etiology.

Acute diffuse glomerulonephritis is for the most part a disease of youth. According

to Seegal and Lyttle, approximately 70 per cent of cases occur before the age of twenty-one. It is relatively uncommon, making up about 0.5 per cent of medical hospital admissions in the United States. This figure is undoubtedly misleading because only cases of overt illness of sufficient severity to warrant hospitalization are included. As will be brought out later, there is good reason to believe that renal involvement may not be clinically evident or particularly alarming in many instances and the majority of cases are probably never recognized.

Classically, the disorder begins abruptly with the appearance of edema which has a curious tendency to collect about the eyes and over the cheeks although in grosser forms all parts of the body may be involved and fluid may accumulate in the serous cavities. At the same time the urinary output diminishes sharply and the urine becomes grossly bloody. Occasionally, however, hematuria is detectable only by microscopy. Proteinuria is almost always found. In association with these evidences of renal dysfunction and water retention a variable elevation of arterial pressure frequently is observed. These changes persist for one or two weeks and then, in about 90 per cent of children and 60 per cent of adults, slowly clear.

Various combinations and permutations of different types of involvement of the kidney and vascular system may occur and produce a variety of clinical states. In a few individuals the renal functional disturbance may be so profound that uremia develops. Acute diffuse glomerulonephritis may be manifested from the outset as the nephrotic syndrome; it seems likely that the

acute loss of enormous amounts of protein in the urine contributes to depletion of plasma albumin and hypoalbuminemia. In such cases hematuria may be minimal or apparently lacking. Occasionally hypertensive "encephalopathy" or cardiac failure may predominate and present difficult problems of diagnosis and management. Even in the more serious cases the prognosis is favorable and appropriate treatment usually has a gratifyingly successful outcome. Nevertheless, from 5 to 10 per cent of the hospitalized patients fail to respond and die as a result of renal insufficiency, heart failure or disturbances of the central nervous system. In a somewhat larger number the disease persists and becomes chronic.

The most important clue to etiology lies in the fact that an upper respiratory infection nearly always precedes the onset of acute nephritis by one to three weeks. Intensive bacteriologic studies have implicated the hemolytic streptococcus as the most frequent infective agent responsible for this antecedent episode. Furthermore, scarlet fever, erysipelas and other streptococcal diseases are frequently complicated by acute nephritis. Indeed, Lyttle found typical urinary changes by Addis count at some time in the course of scarlet fever in all of a series of fourteen children. These observations strongly suggest that the hemolytic streptococcus is concerned in some manner with the pathogenesis of acute diffuse glomerulonephritis. Dr. David Seegal will discuss this aspect.

DR. DAVID SEEGAL: Considerable evidence has accumulated incriminating the hemolytic streptococcus as the chief causative agent of acute glomerulonephritis. Loehlein in 1907 was among the first to point out this relationship and subsequent studies leading to Longcope's comprehensive investigations have lent weight to this opinion.

With Dr. Lyttle and subsequently with Dr. Emily Loeb, we carried out studies on the role of infection in acute nephritis in 116 consecutive patients admitted to the

Babies or Presbyterian Hospital from 1932 to 1937. Eighty-two per cent of the group were under thirteen years of age. This series probably represents the characteristic age distribution in acute nephritis. About three-quarters of the patients gave clinical evidence of an antecedent or progressive hemolytic streptococcus infection. The majority of these infections were of the deep or septic variety unlike the mild pharyngitis associated with the onset of rheumatic fever. Although most of the patients entered the hospital many weeks after the onset of an upper respiratory infection, group A hemolytic streptococci were recovered from the pharynx of 71 per cent of the patients studied. It was impossible on bacteriologic evidence, however, to incriminate the hemolytic streptococcus as an etiologic agent in the remaining 29 per cent. It was necessary, therefore, to search for other evidence of prior infection. With the cooperation of Dr. Heidelberger we found that serum precipitins against several hemolytic streptococcus nucleoprotein fractions could be demonstrated in two-thirds of our patients. However, it was only with the introduction of the antistreptolysin test of Todd that we had a tool to gain the information we sought. In our first series of consecutive patients with acute nephritis, studied in 1933, we found that twenty of twenty-two of the serums contained a sufficiently high antistreptolysin titer to indicate a recent hemolytic streptococcus infection. Serial antistreptolysin determinations carried out subsequently on the serums of several hundred consecutive patients with acute nephritis showed evidence of a group A hemolytic streptococcus invasion prior to the onset of the nephritis in at least 94 per cent of the patients. It is of interest that a considerable number of these patients with unmistakable immunologic evidence of hemolytic streptococcus infection had been described on admission to the hospital as having experienced wet feet, influenza, coryza or intestinal catarrh prior to the onset of the nephritis. Although it cannot be denied that acute glomerulonephritis

may be initiated by other agents, the immunologic evidence indicates that the hemolytic streptococcus is by far the chief instigator.

Before leaving the subject of acute nephritis may we call attention to certain immunologic data which we have collected. The height and duration of the abnormal antistreptolysin titer in patients with acute glomerulonephritis appear to be directly related to the severity, persistence or recurrence of the hemolytic streptococcus infection. However, no such relationship is demonstrable between the antistreptolysin response and the severity or duration of the acute attack of nephritis or the tendency to develop chronic nephritis.

Although accurate figures are difficult to obtain, it is generally stated, as Dr. Bradley mentioned, that about 95 per cent of the acute glomerulonephritis in childhood heals whereas only about 60 per cent of the acute nephritis in adults heals. However, the difference in these figures may be more apparent than real since it is often difficult to differentiate between an initial attack of nephritis and an exacerbation of the chronic form of the disease. Our experience would lead us to believe that some reported episodes of acute nephritis in adults represent exacerbations. Since the latter are manifestations of the chronic state, it is not expected that healing will occur.

Many observations have indicated that patients with healed acute glomerulonephritis are remarkably resistant to second attacks. This is of interest since in rheumatic fever, another disease of proven association with the hemolytic streptococcus, recurrence is common. An opportunity was presented to study twenty individuals clinically, bacteriologically and immunologically during the stage of acute glomerulonephritis, throughout a subsequent healed period and following a later infection with a group A hemolytic streptococcus. Eighteen of the twenty patients experiencing an invasive group A hemolytic streptococcus infection, after healing had been established, failed to demonstrate any significant abnormalities

by urine analysis. Two of the patients experienced an infection proved to be caused by the hemolytic streptococcus in one individual and presumably caused by that organism in the other. Both developed immediate gross hematuria unaccompanied by significant proteinuria. The urine analyses became negative in four weeks and one week, respectively. Not one of the twenty patients studied has developed the chronic form of glomerulonephritis. The nature of this impressive tissue immunity is not known.

Healing fails to occur in the minority of patients with acute nephritis and at the end of six months a subacute phase of the disease is apparent. Although this disease may ultimately heal in a few members of this group, the majority will experience progressive inflammation and degeneration of renal architecture leading to death within a few years. In children the combination of edema, hypertension and nitrogen retention is common in this stage. The clinical and laboratory picture is unlike the nephrotic phase of glomerulonephritis. Longcope suggested that the transition of acute nephritis into the subacute phase was related to persistence of the hemolytic streptococcus infection. This was an attractive concept in view of the close relationship which had been established between hemolytic streptococcus infection and the onset of acute nephritis. However, our clinical and bacteriologic experiences did not permit this generalization. In the presulfonamide days it was not unusual for us to see patients whose acute nephritis healed completely in the face of persistent and angry forms of hemolytic streptococcus infection. Conversely, in other individuals the subacute form of nephritis would progress inexorably in the absence of demonstrable hemolytic streptococcus infection. It could not be denied, however, that the infection preceding the acute nephritis might have set off a chain of immunologic reactions which served to activate the nephritis.

The mechanism for the maintenance of the chronic state of glomerulonephritis is

unknown. Two points of view prevail with respect to the nature of the disease. The one opinion held by Longcope and Ellis is that the disease arises *de novo* and is not a projection of acute hemorrhagic nephritis. This may be the correct view but it is less attractive to us than a second possibility. We share de Wesselow's opinion that the majority of patients with acute glomerulonephritis are not seen by a physician. It is reasonable to assume that a number of such individuals fail to heal their nephritis. In time they will present the clinical picture of the nephrotic phase of chronic glomerulonephritis which Longcope and Ellis might consider as arising *de novo*.

The velocity of development of chronic nephritis has wide limits and attempts to relate certain portions of the natural history of the disease to episodes of infection have yielded variable results. It has been possible, however, to obtain useful data concerning the relation of infection to the exacerbation in nephritis. We followed sixty-eight patients with chronic glomerulonephritis for one to eight years. Twenty-eight exacerbations of the nephritis were observed in thirteen individuals. All thirteen experienced at least one exacerbation preceded by a group A hemolytic streptococcus infection. Eight of the exacerbations followed infections which could not be proved due to this organism. No exacerbation of chronic glomerulonephritis in this series occurred without concomitant infection and in twenty of twenty-eight times this was a proven hemolytic streptococcus infection.

The latent period between the onset of the infection and the exacerbation was from one to four days in the majority of instances. This latent period, as pointed out by others, is much shorter than that seen between the infection and the onset of acute glomerulonephritis. This difference may be of some aid in differentiating the acute from chronic forms of the disease.

A common effect of exacerbations is to produce a transient decrease in renal function. Ten of thirteen patients in our series exhibited one to four such exacerbations. In

six patients no effect on renal function could be demonstrated; four of these six patients, however, experienced other exacerbations in which a transient decrease in renal function occurred. Only one patient developed a permanent decrease in renal function following an exacerbation but the nephritis was in the terminal stage at the time.

Dr. Earle of our group studied the relationship of the serum antistreptolysin titer to the exacerbation in chronic glomerulonephritis and found among other things that when it occurred, the greater the magnitude of the rise in the antistreptolysin titer the greater was the incidence of associated exacerbation in chronic glomerulonephritis. He further found that the exacerbation preceded the onset of the rise in antistreptolysin titer in seven of the eight sufficiently studied episodes.

Apart from overt exacerbations in the course of glomerulonephritis, it is difficult to relate closely the progression of the nephritis to concomitant hemolytic streptococcus infection. Although the carrier state for the hemolytic streptococcus was observed somewhat more frequently in patients with progressive nephritis than in those in the latent stage, the incidence of hemolytic streptococcus infections and exacerbations was similar in both groups. In individual patients a non-progressive phase of the disease would be apparent over a period of years with or without hemolytic streptococcus infection. Subsequently, the velocity of the nephritis would appear to increase in these patients either with or without the presence of demonstrable hemolytic streptococcus infection. It became apparent that a new experimental approach had to be explored to gain information concerning the mechanism of progressive nephritis.

DR. BRADLEY: The evidence set out by Dr. Seegal gives strong support to the view that the hemolytic streptococcus is directly implicated in causing acute nephritis but more crucial evidence is required before we can accept the concept as more than a reasonable hypothesis. It is necessary to

produce the disease experimentally in animals with streptococci and to demonstrate the mechanisms by which these organisms produce renal damage. The experimental production of glomerulonephritis might provide a means of answering the questions raised by Dr. Seegal regarding the factors involved in perpetuating the acute process with the establishment of a chronically active lesion. Dr. Beatrice Seegal will consider these aspects of the problem.

DR. BEATRICE SEEGAL: Attempts to reproduce nephritis in animals by inducing hemolytic streptococcus infection have generally been unsuccessful. For example, Dr. David Seegal and his associates produced a variety of group A hemolytic streptococcus infections in mice, rabbits, dogs, goats and monkeys but never obtained evidence of nephritis. Similar experiments by other investigators have been equally unsuccessful. On the other hand, Doan and his associates have reported that five monkeys of a group receiving intranasal inoculations of both influenza virus and group C hemolytic streptococci developed clinical manifestations of acute nephritis, namely, edema, hypertension and albuminuria. The urinary sediment contained casts and red cells. Two of the animals were sacrificed during the acute disease. Grossly, the kidneys were large and congested. Histologically, there was evidence of tubular damage and the glomeruli showed thickening of the capsular epithelium with occasional leukocytic infiltration.

From the foregoing statements it may be readily understood that the experimental production of nephritis by the technique of producing group A hemolytic streptococcus infection is unsatisfactory. The results obtained in monkeys following group C hemolytic streptococcus infection indicate the possible advantage of using an animal pathogen in such studies.

An experimental technique which employs an immunologic approach does regularly produce an acute and chronic nephritis similar to the disease of man in a number of animal species. Richard Pearce in 1903

prepared nephrotoxic serums (cytotoxins) by immunizing rabbits with dog kidney. The injection into dogs of the resulting rabbit anti-dog-kidney serum produced acute kidney damage in the dog, albuminuria and cylindruria and, at autopsy, histologic evidence of glomerular and tubular damage. In 1920 Wilson and Oliver repeated these observations and obtained more pronounced glomerular lesions than those reported by Pearce. Ten years later Masugi added a most important observation on the natural history of this nephritis. Masugi used both rats and rabbits as test animals. Anti-kidney serums for each species were prepared; rabbits were immunized with the rat kidneys and ducks with the rabbit kidneys. After injection of the specific antisera into the rats or rabbits, the animals were studied for weeks or months. It was then observed that the initial acute nephritis might be followed by a chronic progressive disease even though no further injection of the anti-kidney serum was given. In other words, the acute nephritis instituted by the nephrotoxic serum was followed by a self-perpetuating disease.

These observations on the production of chronic progressive nephritis have been amply confirmed. Smadel and Farr have given a particularly clear picture of the progress of the disease in rats. Within twenty-four to forty-eight hours following the initial injection of the nephrotoxic serum there is albuminuria and cylindruria and there may also be edema and hypertension. This acute phase lasts several days and is then usually followed by improvement which may progress to healing. Often, however, in the course of weeks or months albuminuria and cylindruria increase, hypertension and nitrogen retention develop, there is a plasma protein deficit and anemia and, finally, months after the injection of the anti-kidney serum, the animals die of renal insufficiency. Histologically, in the early stages there is swelling of the intercapillary substance of the glomerular tuft and tubular degeneration. Later there is scarring of the glomeruli and tubules.

The following interesting physiologic data have been obtained from studies in animals rendered nephritic by cytotoxic serum: (1) In rabbits, Ehrlich has reported diuresis and increase in filtration during the first week after the injection of the anti-kidney serum, followed by oliguria on about the eighth day. He reports the lesion as a diffuse cellular proliferation within all the glomeruli. (2) In dogs, Fouts, Corcoran and Page have observed an early increase in the rate of renal blood flow with decreased efficiency of glomerular filtration which they attribute to thickening of the glomerular basement membrane. (3) Smadel and Farr have found that nephritic rats of the Whelan strain maintained on a diet containing 40 per cent protein have a more severe, rapidly progressing disease, whereas those maintained on a diet containing only 5 per cent protein have a less severe disease than do the control nephritic animals maintained on the stock diet containing 18 per cent protein. Nephrotoxic nephritis in the Wistar white rat was uninfluenced by protein in the diet. (4) Smadel and Swift report that the natural history of cytotoxic nephritis in the Long-Evans and Wistar rat is somewhat different from that in the Whelan strain. Rats of the Long-Evans strain show a decrease in clinical signs between the thirtieth and seventieth day after injection of the nephrotoxic serum and then progression to chronic nephritis. The Wistar rats have a less marked acute nephritis and a period of apparent healing before chronic nephritis develops. In the Whelan strain acute nephritis progresses directly to the chronic state. They interpret these observations as indicating an inherited difference in susceptibility to nephrotoxin.

Nephrotoxic nephritis in the rat is relatively organ-specific. Kidney damage does not follow the injection into rats of non-specific antisera prepared by immunizing rabbits with such antigens as rat serum, erythrocytes, heart, liver and testicle. However, Dr. Emily Loeb and I have found that the serum of rabbits which have been immunized with rat placenta is nephrotoxic

and gives rise to chronic progressive nephritis as well as to abortion. This is significant in view of the association of renal pathology with the toxemias of pregnancy. Inter-current pregnancy also has a deleterious effect upon the course of chronic nephritis in man.

The mechanism responsible for the development of cytotoxic nephritis naturally excites great interest. Two pieces of evidence suggest that the antibody concerned in producing nephrotoxic nephritis is directed against glomeruli. Pressman and his associates have iodinated the globulin fraction of rabbit anti-rat-kidney serum and anti-mouse-kidney serum with iodine containing tracer amounts of I^{131} . Radioautographs of the tissues from rats or mice injected with this iodinated antibody have demonstrated that the localization of the radioactivity and presumably of the antibody was in the glomeruli of the kidneys. Other evidence to support the importance of antibodies to glomeruli is that furnished by Ferrebee and his associates (personal communication). A method has been developed for obtaining rat kidney glomeruli in relatively pure state. These have proved capable of absorbing the nephrotoxic agent from antisera prepared by immunizing rabbits with the whole rat kidney.

Kay, in an attempt to explain the disease in rabbits, noted that in this animal, in contrast to the rat, there is a latent period of a week before albuminuria develops following the injection of the nephrotoxin, duck anti-rabbit-kidney serum. He suggested that the antibody-bearing foreign antigen (duck immune globulin) was anchored to the kidney by its immune reaction with this organ. Subsequently, after a period of time corresponding to the latent period observed, antibody to duck globulin developed. This in turn reacted with the duck globulin attached to the rabbit's own kidney cells and acute nephritis resulted. Support for this point of view was obtained by giving x-ray treatment to rabbits injected with the nephrotoxin. This prevented the development of rabbit antibody to duck globulin.

It also prevented the development of nephritis.

This explanation for the acute nephrotoxic nephritis in rabbits cannot be used to explain the disease in rats since there is practically no latent period between the injection of nephrotoxic serum and the onset of signs of acute nephritis. In neither animal is the progressive nature of the chronic disease explained. As Smadel and Swift have well stated, it is difficult to believe that the foreign nephrotoxic serum can persist in the rat's body for many months and contribute to the recurrence or progression of renal disease. These authors suggest that both residual scarring of the glomeruli and "excessive or abnormal stresses and strains to which tubules are subjected" may contribute to the evolution of the chronic nephritis. Another explanation, an immunologic explanation, for the chronic nephritis would assume the possibility of auto-antibody production. Once the kidneys have been damaged by the cytotoxins one may conceive that the kidney proteins are sufficiently altered antigenically to stimulate antibody production. These auto-antibodies, in turn, would damage more kidney tissue and thus give rise to more tissue capable of further stimulating the production of damaging antibodies.

If, in the etiology of human nephritis, one is to implicate a mechanism similar to that operating in cytotoxic serum nephritis, it would appear necessary to assume the production of auto-antibodies to kidney tissue in the presence of hemolytic streptococcus infection. Certainly the patient with nephritis has not been injected with antibodies to human kidney and unless he has contrived to produce some of his own there can be no relationship between the pathogenesis of his disease and the cytotoxic nephritis described in experimental animals. Evidence that antibody to kidney tissue may play a role in human nephritis is furnished by Lange and his associates. In the sera of fifty-one nephritics in all stages of the disease circulating antibodies to human kidney were present, as demonstrated by the

collodion particle technic in 72.7 per cent. Higher titers and greater incidence of positive reactions were obtained in cases in which patients were tested after the first month of the disease.

Dr. David Seegal and his associates have attempted to demonstrate experimentally that the hemolytic streptococcus is able to render kidney antigenic for the homologous animal species. The kidneys of both rabbits and rats were exposed to cultures of Group A hemolytic streptococci and were then implanted in normal rabbits or rats. In some experiments fresh kidney tissue was added to broth inoculated with the hemolytic streptococcus and incubated twenty-four hours at 37°C. In other experiments young broth cultures were injected into the renal artery of excised kidneys, thus perfusing the kidney with streptococci. In either case the kidney tissue, saturated with hemolytic streptococci, has been implanted in the peritoneum of animals of the same species. Nephritis has not been obtained by this method.

On the other hand, the Caveltis have succeeded in demonstrating the production of auto-antibodies in both rabbits and rats and have obtained nephritis in the latter animal. They injected these animals with homologous kidney ground and suspended with large numbers of *ether-killed* hemolytic streptococci which stimulated the production of auto-antibodies to the kidney tissue. In the case of the rat, this has been followed by the development of chronic nephritis similar in course and disease picture to that which results from the injection of a prepared rabbit anti-rat-kidney serum. This method for obtaining nephritis is apparently beset with difficulties since Humphrey, using an almost identical technic, has been unable to produce the disease.

The implication of these experiments described by the Caveltis is that the hemolytic streptococcus is able to alter the antigenicity of the kidney so that it can induce auto-antibodies which react with the kidney to produce nephritis. The kidney tissue so

injured may stimulate further anti-kidney antibodies which injure more kidney and so establish a self-perpetuating disease. It must be emphasized that there is no direct evidence in support of such an etiology for nephritis in man and certainly arguing by analogy with animal experiments is hazardous. However, irrespective of the relationship between human and animal nephritis the experiments described serve a very useful purpose. A method is at hand which enables the investigator to study the effects of disturbed renal physiology in animals with renal disease closely simulating human chronic nephritis.

DR. BRADLEY: Even though our knowledge of etiology is incomplete, we seem justified in taking the view that acute diffuse glomerulonephritis is precipitated by some disorder of immune mechanisms in streptococcal infections. Such a disorder may well be susceptible to therapeutic and prophylactic attack. The data obtained from investigations of renal pathology and physiology give further support to this belief since they indicate that acute nephritis is primarily inflammatory and that marked changes may be completely reversible.

The focal point of damage appears to lie in the glomerulus. In the more severe cases there is diffuse involvement of nearly all glomeruli with thickening and reduplication of the basement membrane, proliferation and swelling of the capillary endothelium and infiltration with leukocytes so that cellularity increases strikingly. Later the capsular space contains a fibrinous exudate which becomes organized as "crescents" and is responsible for the formation of adhesions between capillary loops and between the tuft and the capsular wall. Despite marked engorgement of the kidney as a whole, the capillary loops are often empty and collapsed. Marked obstructive distortion of capillaries and proliferation of endothelium may contribute to this by preventing adequate perfusion. The tubules, too, are affected but to a much less striking degree. Here and there desquamation of tubular

cells may be found and scattered cells appear to be undergoing necrobiosis. Jean Oliver has called attention to inflammatory changes in the interstitial tissue. The subsequent alterations which may occur with progression do not concern us today; it is remarkable, however, that the widespread lesion of acute nephritis may clear altogether leaving no demonstrable residual damage.

On the whole, the derangements of renal function may be correlated quite well with the morphologic abnormalities. The urinary findings conform with the notion that a glomerular capillary lesion results in filtration of larger molecules than normal, thus permitting albumin and even globulins to enter the filtrate in large amounts. The hematuria is easily traceable to capillary bleeding since erythrocytes may be found within the glomeruli. Red cell casts are obviously derived from masses of red cells packed in the lower reaches of the convoluted tubules and in the collecting ducts, following concentration by the tubular reabsorption of water. Likewise, the demonstrable reduction in glomerular filtration rate, measured by inulin or mannitol clearances, may be ascribed to thickening of the glomerular membrane and/or inadequate perfusion of glomeruli. In Table 1 clearance data collected in studies of twelve patients suffering from acute diffuse glomerulonephritis, as soon as possible after onset, show the extent to which filtration may be impaired, confirming earlier work by Earle, Taggart and Shannon. It will be noted that filtration returns to normal or almost normal values with healing, as in M. B. and in L. L. (Fig. 1.)

This *disturbance of filtration* readily accounts for the tendency to retain nitrogenous wastes. Azotemia, varying in severity and affecting all components of the non-protein nitrogen, is closely correlated to the degree of filtration defect, although augmented degradation of protein may play a part in determining the blood levels. The decreased glomerular filtration is associated with a lesser defect in tubular reabsorption and a

glomerulo-tubular imbalance results which causes disproportionate reabsorption of water and salt, thus contributing directly to retention of water and formation of edema.

In addition to disproportionate renal reabsorption of salt and water by the tubules

blood into the tissue spaces. Many measurements of the protein content of edema fluid appear to bear this out since protein concentrations approaching those of plasma have been reported. However, tissue fluid samples are easily contaminated with plasma

TABLE I
RENAL FUNCTION IN ACUTE DIFFUSE GLOMERULONEPHRITIS*

Subject	Sex	Age	Glomerular Filtration Rate	Renal Plasma Flow	Filtration Fraction	Extraction Per Cent	Renal Blood Flow	Tm _{PAH}	Azotemia	Edema	Blood Pressure	Estimated Days after Onset
M. B.	F	52	17.4 59.6 84.8	62.6 312.6 406.0	27.9 19.0 21.2			39.9 53.4	Yes Yes No	Yes Yes Yes	164/74 156/95 144/84	7 11 20
F. C.	M	11	48.0 34.5	363.0 436.0	13.2 7.9	82.9	965	29.4 29.5	Yes Yes	Yes Yes	140/75 124/80	10 20
M. C.	M	39		505.0		76.5	1120		Yes	Yes	150/90	24
J. S.	F	6	13.8	112.5	12.4			8.2	Yes	Yes	172/120	10
I. A.	F	25	28.4	327.0	8.7	47.0	932		Yes	Yes	145/95	39
M. S.	M	47	67.0	653.0	10.2	76.4	1278	80.9	Yes	Yes	196/104	9
G. M.	F	7	34.0	251.0	13.5			15.4	Yes	Yes	120/80	14
E. S.	F	14	41.1	405.0	10.4	79.8	824		No	Yes	135/105	20
A. S.	F	37	66.6	598.0	11.1	82.6	1226	54.0	Yes	Yes	150/80	26
L. P.	M	52	90.0	500.0	17.5	69.4	1021	60.2	No	No	234/138	49
H. C.	M	47	157.2	1320.0	11.7	100.0	1320	72.2	No	No	100/60	64
T. B.	M	15	62.8	402.5	15.4	94.0	757		No	No	108/72	16
Normal Range			100-150	520-800	17-21	89-100	800-1400	65-90				

* These subjects are arranged in order of severity of the disease process as judged upon clinical grounds. The figures were obtained in studies of patients with clear-cut acute diffuse glomerulonephritis at the Evans Memorial Hospital, Boston, Massachusetts, and the Presbyterian Hospital, New York. Each is an average of two or more determinations. Clearance measurements were made according to the methods described at length by H. W. Smith and his co-workers (see Lectures on the Kidney, Lawrence, Kansas, 1943. University of Kansas Press). The PAH extraction was determined by the method described by Bradley (Tr. Josiah Macy, Jr. Conf. on Factors Reg. Blood Pressure, 1). Normal values are taken from these sources. The headings are as follows: Glomerular Filtration Rate, cc. per minute, measured by the mannitol clearance; Effective Renal Plasma Flow, cc. per minute, measured by the PAH clearance; Filtration Fraction, per cent, equal to Glomerular Filtration Rate/Renal Plasma Flow; Extraction per cent, renal PAH extraction, Renal Blood Flow, cc. per minute, equal to Renal Plasma Flow/Extraction per cent $\times 100$ —hematocrit; and Tm_{PAH}, maximal tubular excretion of PAH, mg. per minute.

and, in some patients, hypoalbuminemia, less clearly defined factors often contribute to edema formation in acute nephritis. It is evident that the reduction of water output is directly linked to the accumulation of fluid in the tissues; possibly, however, this phenomenon is secondary in nature. The sudden appearance of facial edema without evidence of weight gain is often cited in support of the belief that acute nephritis is part of a widespread capillary disease in which increased capillary permeability results in a loss of protein and water from the

from accidentally punctured capillaries. More recent determinations by Stead and others, with refined techniques, have yielded lower values, less than 0.4 Gm. per cent, comparable to those obtained for the edema fluid of heart failure. This finding certainly suggests that capillary permeability is not increased but does not constitute conclusive evidence since it depends upon small samples which are taken from areas of gross edema and may not be representative of edema fluid in general. Recent studies in this country and abroad have disclosed

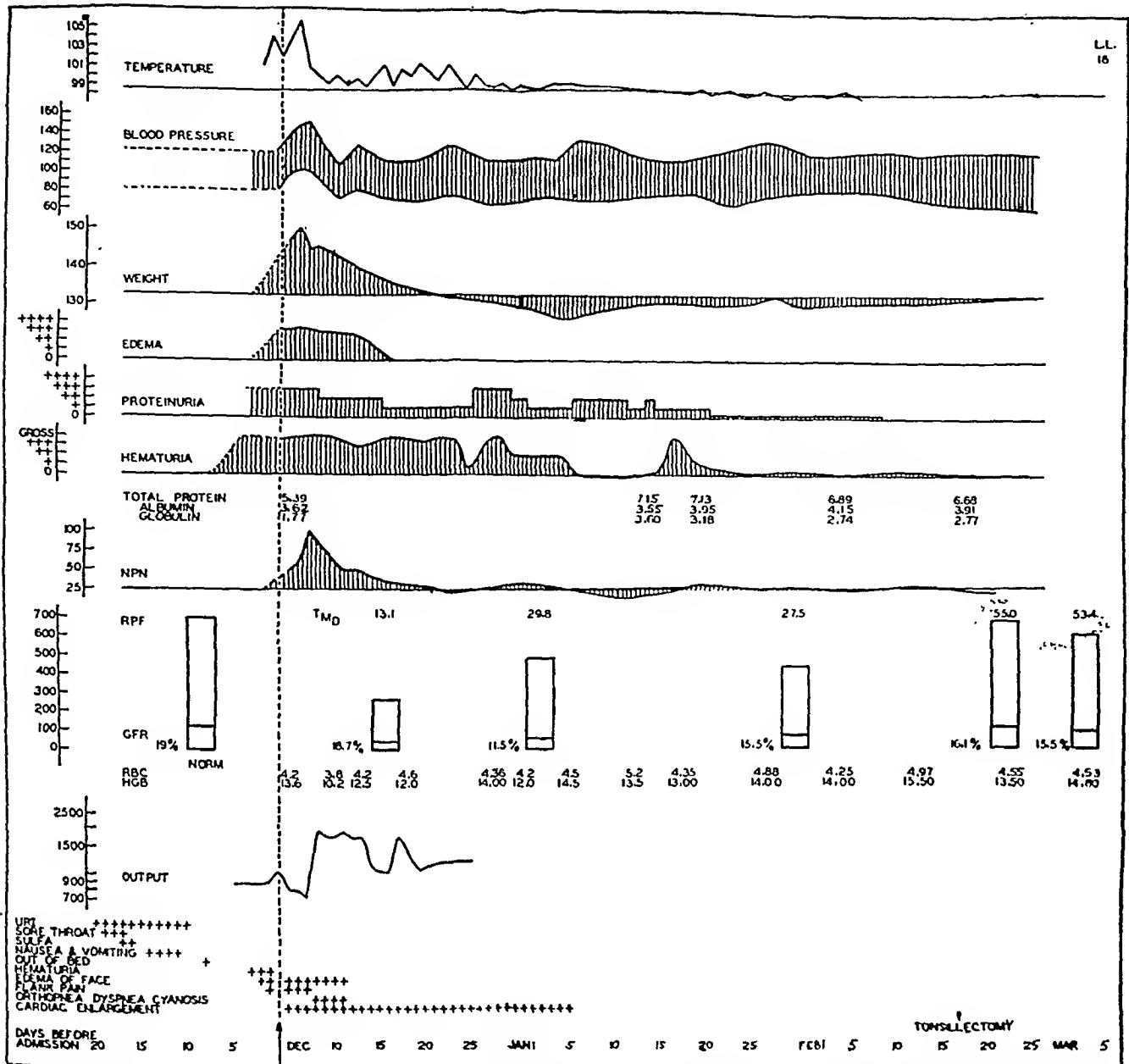


FIG. 1. Clinical course in acute diffuse glomerulonephritis. L. L., a seventeen year old white boy, complained of grossly bloody urine, severe flank pain, weight gain, facial edema and fever of three days' duration. Twenty days prior to admission to the hospital he suddenly became very ill with an upper respiratory infection. He remained in bed for almost two weeks. The body temperature was elevated for four days after hospitalization and then fell abruptly to normal in association with the sudden development of signs of congestive heart failure, including orthopnea, dyspnea and cyanosis. This episode was preceded by a rapid elevation in blood pressure, weight and serum NPN. Digitalization and oxygen therapy were followed by relief of symptoms, by a diuresis and a fall in NPN and blood pressure. The body weight returned to normal less rapidly and the edema slowly cleared. At this time there was a marked reduction in the renal function, including glomerular filtration rate and effective renal plasma flow. The filtration fraction was normal. The maximal tubular excretion of diodrast was also greatly reduced. With recovery, the proteinuria and hematuria slowly cleared, the heart size and electrocardiogram returned to normal and the kidney function gradually improved. Recovery appeared to be complete three months after onset, following removal of chronically infected tonsils. Even at this time, however, the filtration fraction and the filtration rate were significantly reduced.

an apparent increase in plasma volume early in the course of acute nephritis indicating an expansion of the extracellular water as a whole, with coincidental edema.

In many instances heart failure is another important contributing factor in the accu-

mulation of salt and water. Arterial hypertension is but one cause of cardiac failure in acute glomerulonephritis and growing evidence indicates that failure may occur when elevation in blood pressure is but slight or absent. Enlargement of the heart occurs not

infrequently during acute nephritis and Dr. John Dean has reported three cases from this clinic in which it persisted for many months in the absence of significant hypertension. Electrocardiographic abnormalities are encountered at some time during the course of many cases, from 60 to 90 per cent in different series. Rubin and Rapoport and other workers have stressed the frequency with which T_1 is inverted or low in association with depression of ST_1 . Reciprocal changes are found in the third lead. Clockwise deviation of Wilson's ventricular gradient has been reported by La Due and Ashman. Since these effects are correlated with cardiac enlargement rather than hypertension, they suggest that rapid dilatation of the heart might be a causative factor. Most investigators have failed to find distinctive pathologic changes in heart muscle although Gore and Saphir have described serous myocarditis in sixteen of one hundred sixty patients dying in the course of acute nephritis. Possibly expansion of the plasma volume operates in this instance, as Stead has suggested, to throw an added strain upon the myocardium (which may be affected adversely in other ways by the disease), precipitating the rapid onset of decompensation.

Certainly one frequently observes the sudden onset of symptoms and signs of congestive failure some time after the appearance of peripheral edema. Such an instance is illustrated by L. L. (Fig. 1), a boy of seventeen in whom edema, hematuria, proteinuria and azotemia were observed at least one week prior to the rapid development of orthopnea, dyspnea and cyanosis, cardiac enlargement and pulmonary edema. Digitalization and oxygen therapy were followed by improvement including a fall in the blood pressure and diuresis. The heart size and electrocardiogram returned to normal much more slowly despite the early correction of blood pressure levels. This sequence suggests the priority of water retention and hypervolemia in the chain of events, serving to focus attention upon the kidney as the chief source of difficulty. In

addition, it is evident that heart failure contributed to the impairment of renal function in this case since the blood non-protein nitrogen concentration rose sharply with the onset of failure and fell slowly toward normal with recovery. Perhaps a superimposed disturbance of the renal circulation accounts for this.

The renal blood flow may be measured in acute nephritis as the p-aminohippurate (PAH) clearance corrected by the values for the renal PAH extraction and arterial hematocrit. The extraction of PAH is determined by measuring the PAH concentration in both peripheral arterial or venous blood and renal venous blood obtained from the left renal vein by catheter. The difference between these values divided by the figure for PAH concentration in arterial blood yields a value for the percentage of PAH removed by the kidney from the blood perfusing it. Corrected values for renal blood flow obtained in nine patients by this method are tabulated in Table 1. All were at the upper limits of normal or slightly in excess of normal, denoting a relative or absolute hyperemia of the kidney. This finding is consistent with inflammation and may cast light upon the occasional complaint of flank or back pain which may be throbbing in nature and sufficiently severe to require the use of analgesic agents. In the more severe cases with marked oliguria or anuria the blood flow is probably greatly reduced as a result of obstruction to flow through glomerular capillaries and increased intrarenal tension. Very low diodrast or PAH clearances (effective renal plasma flow), (M. B. and J. S., Table 1; L. L., Fig. 1) which are very difficult to explain in any other way are found in such cases. Even so the reduction in effective renal plasma flow is much less than that in glomerular filtration rate. Hence, the filtration fraction, or percentage of plasma filtered during passage through the kidney, is nearly always reduced below normal. (Table 1.)

The PAH extraction was found to be depressed below the normal range of 89 to

100 per cent in every instance but two (H. C. and T. B.) who had recovered completely according to the clinical evidence. This phenomenon may be interpreted as indicating either arteriovenous shunting of blood or perfusion of damaged tubular tissue. The fact that the maximal tubular excretion of diodrast (L. L., Fig. 1) or PAH (Table 1) is usually reduced favors the latter explanation. Despite the relatively slight anatomic change in tubular cells it is apparent that significant functional alterations have occurred.

Arterial hypertension was observed in most of the cases reported here, regardless of the presence of renal hyperemia relative to the mass of functioning tubular tissue. It is impossible to say whether the change in renal blood flow corresponded to the change in blood pressure since control values were obviously impossible to obtain. There is little evidence that vasoconstriction occurred in the kidney. The cause of hypertension in acute nephritis remains unexplained and insufficient evidence is at hand to warrant speculation. Certainly the various complications of hypertension may have a further detrimental effect upon renal function.

The convulsive seizures and other neurologic disturbances which may have serious consequences in patients with acute nephritis are believed to arise as a result of hypertensive cerebrovascular disease. These manifestations are clearly correlated with the severity of the arterial hypertension and they resemble the "encephalopathic episodes" observed in the course of essential hypertension. Whether hemorrhage, edema or possibly small thromboses are chiefly responsible remains disputed.

Hematologic disorders are occasionally present. In a few patients a severe bleeding tendency will give rise to hemorrhage into the skin, serous cavities, bowel or urinary tract. No satisfactory explanation for this phenomenon has been advanced. Anemia may develop in patients with more severe forms of acute nephritis but is much more common in association with advanced renal failure in the chronic form of the disease.

According to recent work by Emerson, both increased blood destruction and impaired blood formation are involved.

In this clinic we have attempted to point out the paths along which progress has been made in clarifying the basic mechanisms of change in acute diffuse glomerulonephritis. Perhaps one of these will prove to be the way to a more complete understanding and more effective therapy of the disease. For the present, treatment is symptomatic and supportive according to principles that Dr. Loeb has agreed to outline briefly for us.

DR. ROBERT F. LOEB: In the patient exhibiting mild acute glomerulonephritis without hypertension, edema or nitrogen retention, no specific therapy is indicated. In the presence of significant hypoalbuminemia or overt edema, intake of sodium salts should be sharply restricted. In fulminating cases exhibiting hypertension and edema associated with marked oliguria it is probably well to restrict fluid intake to the amount excreted by the kidneys plus that lost through insensible perspiration, about 1,200 cc. During this period, which rarely exceeds a few days, it is a good plan to conserve body protein by incorporating 100 to 150 Gm. of carbohydrate in the diet and to exclude all sodium salts from the diet and infusions. Congestive heart failure should be treated by conventional methods.

In the presence of overt streptococcal infection penicillin should be employed although, as indicated by Dr. Seegal, cure of the streptococcal infection probably has little influence *per se* on the course of the nephritis.

STUDENT: How long should the patient be kept in bed?

DR. LOEB: Bed rest should be continued as long as hypertension, heart failure or edema persist. It might be desirable to keep the patients at rest until all the urinary abnormalities have disappeared but unfortunately this is not feasible since albuminuria and hematuria may continue for many months.

STUDENT: What about diuretics?

DR. LOEB: Diuretics have no place in the management of acute glomerulonephritis.

STUDENT: Does potassium poisoning occur in the acute phase of glomerulonephritis?

DR. LOEB: It is probably rare.

STUDENT: Will you comment on the management of convulsions?

DR. LOEB: The management of convulsions consists of sedation, including perhaps the intravenous or intramuscular administration of magnesium sulfate. Lumbar puncture usually does not give convincingly beneficial results.

SUMMARY

DR. FREDERICK K. HEATH: In this clinic emphasis was placed on the relationship of the group A hemolytic streptococcus to glomerulonephritis, certain immunologic mechanisms which might be operative therein, and the pathologic physiology of the acute disease.

Acute glomerulonephritis begins ordinarily one to three weeks following an upper respiratory infection when some combination of the clinical symptoms of hematuria, proteinuria, edema and hypertension appears. The infection is more apt to be deep-seated than superficial although this is not invariable and areas other than the upper respiratory tract may be the site, e.g., wound infections, erysipelas. Throat cultures which are obviously taken when the infection may have subsided are positive for the hemolytic streptococcus in 70 to 80 per cent of cases. Serum precipitins to streptococcus nucleoprotein fractions are found in a proportionate number of cases but antistreptolysin titers give a still higher percentage of positives, being elevated significantly in 90 per cent of cases. The degree of antistreptolysin titer elevation is correlated with the severity of the streptococcus infection and not with the severity of the nephritis. In exacerbations of chronic nephritis, on the other hand, there does appear to be a correlation between the severity of the nephritis and the magnitude of the antistreptolysin titer. Children are more commonly involved than

adults and perhaps the majority of cases in either group never come to medical attention. Over 90 per cent of children heal acute nephritis and thereafter remain immune but only about 60 per cent of adults achieve this favorable outcome.

Individuals with chronic nephritis show evidence of hemolytic streptococcus infection prior to an exacerbation in about 70 per cent of cases. Here the time interval between infection and nephritis is greatly reduced, usually being one to four days. Often there is a demonstrable decrease in renal function with exacerbations but this may be only transient or may not be clinically measurable at all. Aside from this, the factors which make for the development of the chronic disease and determine its velocity are not well understood. There is no relationship between continuing infection and progressive nephritis.

In this dilemma the possibility of auto-antibodies has been raised. The production of nephritis, both acute and chronic, in small animals by the use of nephrotoxic sera (anti-kidney or anti-placental) is well established. In monkeys, after a mixture of group C hemolytic streptococcus plus influenza virus was given intranasally, nephritis has been produced; in no animals has nephritis followed the administration of group A hemolytic streptococci. Recently, however, following injection with a mixture of ether-killed hemolytic streptococci and ground kidney, chronic nephritis and auto-antibodies have been demonstrated in the rat. While there is no implication that a similar process exists in human nephritis, the analogy suggests that the streptococcus might so change the kidney that it serves as an antigen to produce auto-antibodies. These in turn react with the kidney to produce nephritis; the damaged kidney again stimulates more auto-antibodies producing further nephritis. In this way a chronic progressive disease might ensue.

The pathologic process of acute nephritis involves chiefly the glomeruli and to a lesser extent the tubules and interstitial tissue. Hematuria, proteinuria and reduction in

glomerular filtration rate are all explained by the glomerular involvement. Nitrogen retention results from decreased filtration. The tubules are able to handle the reduced glomerular filtrate relatively more effectively with a consequent retention of water and salt. Hypervolemia, low serum albumin and possible increase in capillary permeability all favor edema formation. Cardiac failure when present may contribute to this cycle as it may in part be precipitated by it. Hypertension is not essential for the

cardiac enlargement and, like the anemia, remains unexplained; both tend to accentuate the renal and cardiac abnormalities.

Renal blood flow is in the normal range as might be expected with the hyperemia of inflammation. Renal extraction is reduced probably because of tubular damage. The reduction in renal plasma flow is often not as marked as that in glomerular filtration rate, hence, the filtration fraction is uniformly decreased. Table 1 illustrates these findings.

Clinico-pathologic Conference

Chronic Pleurisy and Peritonitis*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

S B., (History No. 114547), a white, married accountant, forty-four years of age, entered the Barnes Hospital for the first time on May 29, 1944, complaining of stiffness and swelling of the neck. The family history was irrelevant. The patient had had a chronic morning cough productive of thick white sputum. He had also experienced frequent, spontaneous nose-bleeds and on a number of occasions had had abdominal cramping relieved by the passage of flatus. Otherwise his general health had been good. Seven weeks before entry the patient developed a painful left lower tooth which was extracted. Two days later his temperature rose slightly and he noted swelling of the left side of the neck extending down to the left anterior chest. Although over the course of ten days the swelling subsided and the patient became symptom-free, he was admitted to the hospital for study.

At the time of entry his temperature was 36.7°C., pulse 72, respirations 18 and blood pressure 120/80. The patient appeared well. No generalized glandular enlargement was noted. There was a congenital defect in the right retina. Examination of the neck, chest and heart was normal. The liver edge was palpable 2 cm. below the right costal margin on deep inspiration and the spleen could be felt 4 cm. below the left costal margin. The remainder of the physical examination was negative.

Laboratory findings, including a complete blood count, urinalysis, stool examination, blood Kahn test, blood amylase, circulation time and chest roentgenogram, were within normal limits. The venous pressure

in the arm was 205 mm. of saline and in the femoral vein, 145 mm. of saline.

The patient left the hospital on June 1, 1944, without a definitive diagnosis having been made. He re-entered the hospital on April 21, 1945. He had been well in the interval until two months before admission when there was an onset of gradual weight loss, vague abdominal pain and mild dyspnea on exertion. His symptoms continued, and he consulted his private physician who noted signs of fluid in the left chest and referred the patient to the hospital.

Physical examination revealed a lymph node in the left supraclavicular fossa measuring 2 by 2 cm. Signs of fluid in the left chest were apparent. The remainder of the physical examination was not remarkable. Routine laboratory studies were normal. Many sputum smears for acid-fast organisms were negative. Chest films revealed encapsulated fluid in the left pleural cavity; some of the fluid apparently was in the interlobar fissure.

Soon after admission a thoracentesis was performed, and 1,000 cc. of blood-tinged fluid were removed. The fluid had a specific gravity of 1.018. It was inoculated into a guinea pig which showed no pathologic lesions at autopsy six weeks later. Cell blocks made from pleural fluid revealed many large multinucleated cells extremely suggestive of Dorothy Reed cells; a presumptive diagnosis of Hodgkin's disease was suggested. Bronchograms were normal. The patient left the hospital on May 18, 1945, and subsequently was given twelve roentgen ray treatments to the left chest.

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

He felt quite well until two months before his third admission when he developed a dull aching pain in the left lower chest which was aggravated by heavy lifting, twisting his trunk and lying on his left side but not by coughing or deep breathing. The patient had a mild chronic cough which was productive of a moderate amount of mucoid sputum and he complained of abdominal discomfort characterized by sharp cutting pains in the left upper quadrant. There was also some lower abdominal cramping which he attributed to constipation. During the interim between admissions he had lost no weight.

When he was admitted on December 2, 1947, his temperature was 36.5°c., pulse 78, respirations 20 and blood pressure 125/70. The significant physical findings included dullness to percussion, diminished tactile fremitus, diminished breath sounds and a few crepitant rales over the left lower lung field. The remainder of the physical findings were unchanged from those recorded earlier. Numerous laboratory studies were all negative except for the chest film which showed signs of old pleurisy at the left base and left apex. There was a questionable small amount of fluid in the left pleural cavity but because of overlying shadows the left lower lung field could not be adequately visualized. A gastrointestinal series and a cholecystogram were within normal limits. Bronchoscopy was performed but no abnormal findings were noted in the tracheobronchial tree. A diagnosis of chronic pleurisy was made and the patient was discharged on December 11, 1947.

His cough decreased as did the discomfort in the left chest. About three weeks after discharge, however, the chest pain recurred and was more severe than it had been previously; the patient was admitted for the fourth time on January 9, 1948. Physical findings and laboratory data were no different from those noted previously. Soon after admission the patient was subjected to an exploratory thoracotomy under general anesthesia. A section of the seventh rib

was removed and a pocket containing fluid was entered. About 50 cc. of clear, yellow fluid were aspirated and penicillin was instilled into the cavity. The pleura was biopsied; microscopic examination revealed only the changes of chronic inflammation. No tumor cells were seen. The patient had an uneventful postoperative course and during his entire admission, as on the two previous ones, he was afebrile. He was discharged on January 22, 1948, with a diagnosis of pleural effusion, etiology unknown.

He continued to have intermittent pain in his left chest. In February, 1948, marked localized epigastric pain, which came on particularly during meals, appeared. It was unassociated with any other gastrointestinal symptoms or signs until his abdomen began to swell. When he saw his physician three weeks before his fifth admission, signs of ascites were detected and on July 3, 1945, he re-entered the hospital.

At that time his temperature was 37°c., pulse 100, respirations 20 and blood pressure 120/80. The patient now appeared chronically ill. Examination of the chest was as previously noted. The abdomen was distended, but no signs of fluid were demonstrable. The liver extended 6 cm. below the right costal margin. Bleeding hemorrhoids were present; otherwise, the physical examination was not remarkable. Laboratory findings revealed a normal blood count except for a slight left shift in the differential. Numerous liver function studies were normal. Intravenous pyelograms were negative. Sigmoidoscopy was performed and no abnormalities were found. The abdominal bloating and cramping gradually decreased and disappeared but the patient continued to have pain in his left chest. An enlarged lymph node in the right anterior cervical region was removed but on microscopic section showed only chronic lymphadenitis. The patient was discharged unimproved on July 17, 1948.

He continued to have constant dull pain in the left lower chest and occasional sharp

transient pain in the same area. His appetite became poor and he lost 5 pounds. The hemorrhoids became large and bled considerably. A persistent itching eruption appeared over the anterior chest and arms. The patient was re-admitted on August 12, 1948, for nitrogen mustard therapy.

At the time of entry the temperature was 36.5/c., pulse 84, respirations 12 and blood pressure 120/80. Signs over the left lung were attributed to thickened pleura. The abdomen was tense, with signs of ascites. No other new findings were observed.

The red blood cell count was 3,650,000 with 9.8 Gm. of hemoglobin. The white cell count was 5,050, the differential showing 3 per cent stab forms and 72 per cent segmented forms. The urinalysis, thymol turbidity test, cephalin-cholesterol flocculation test, total and fractional proteins, serum phosphorus and alkaline phosphatase were all within normal limits. The patient received 6 mg. of nitrogen mustard intravenously on four successive days and on the fifth day abdominal paracentesis was performed. Twenty-four hundred cc. of grossly bloody fluid were removed. The fluid had a specific gravity of 1.018, a total protein of 4.5 Gm. per cent and there were 2,800,000 red cells per cc. Cultures of the ascitic fluid were negative for bacteria and fungi; guinea pig inoculation also was negative. Cell block sections showed numerous endothelial cells but no tumor cells. After paracentesis the patient was noted to have both a large liver and a large spleen. During his first few hospital days the temperature was 38°C.; following paracentesis it rose to 39°C. and then fell to normal. The patient left the hospital on August 20, 1948.

During the month which elapsed between his sixth and seventh admissions the patient continued to complain of anorexia, weight loss, pain in his left chest, constant dull aching in the upper abdomen and generalized cramping abdominal pains and distention. In addition he was troubled with marked constipation, bowel movements occurring only once every five to seven days. He had occasional mild chills.

He entered the hospital for the last time on September 20, 1948, at which time his temperature was 36.6°C., pulse 92, respirations 20 and blood pressure 110/70. The patient was poorly nourished and appeared chronically ill. The scars from his previous operative procedures were healed. The skin was quite pallid. There was no generalized enlargement of the lymph nodes. Examination of the upper respiratory tract was within normal limits. Examination of the chest revealed limitation of motion on the left side where diminished tactile fremitus dullness and distant breath sounds were noted. The heart was not enlarged. A grade II, blowing, systolic murmur was heard over the pulmonic area. The abdomen was distended and quite tense. No organs or masses could be felt. Small hemorrhoids were noted. No edema was present.

The laboratory findings were as follows: Red cells, 3,900,000; hemoglobin, 9.8 Gm.; white cells, 6,100; differential count: normal. Urinalysis: negative. Stool examination: negative. Electrocardiogram: tendency to right axis deviation.

Following admission to the hospital the patient was given several blood transfusions and an exploratory laparotomy was performed. When the peritoneum was opened, bloody fluid was visible. Diffuse adhesive peritonitis was the most striking finding; all of the viscera were matted together, so much so that neither the spleen nor the liver could be palpated. Two sections of tissue were removed from the parietal peritoneum which felt nodular. Tissue was also removed from the mesentery of the small intestine. Microscopic sections subsequently showed only the changes of chronic inflammation. Sections were also taken from retroperitoneal lymph nodes. Microscopic study of these revealed complete obliteration of the architectural pattern with prominent fibrosis and relatively acellular connective tissue. Plasma cells were abundant and a few eosinophiles were seen. The most common cell was large with a vesicular nucleus and pink cytoplasm. At times rather prominent nucleoli were

seen and in some areas it was thought that the cells resembled Reed-Sternberg cells, but no definite diagnosis could be made. The patient withstood the operative procedure well. He received the usual supportive measures including parenteral fluids and blood. His appetite remained poor. After recovery from the surgical procedure he received 7,000 roentgen units to the abdomen. Despite transfusions, moderate anemia persisted. Following x-ray therapy the red blood cell count was 2,880,000, the hemoglobin 7.6 Gm. and the white cells, 2,150. The differential was normal. Although there was inadequate intake of food, the patient's condition for several weeks following operation showed little change. The serum proteins remained normal until early in December, several months after admission, when they were found to be 4 Gm. per cent. The albumin was 2.7 Gm. per cent and the globulin 1.8 Gm. per cent. Blood chlorides were 94 mEq./L. These studies were made about the time that the patient developed pitting edema of his thighs and ankles. Anorexia persisted and frequent spells of vomiting occurred. On December 15th the patient had a sudden onset of sharp pain in the right chest posteriorly, associated with shortness of breath and increased cough. There was no fever. Physical examination revealed dullness and absent breath sounds over the right base posteriorly and a loud friction rub was audible over the lower half of the right chest. A chest film revealed an area of triangular infiltration which was interpreted as pneumonia. Because of the possibility of pulmonary infarct, however, Dicumarol therapy was instituted. The patient was also given antibiotics. Despite these measures he became weak and irrational. The pulse became feeble and his blood pressure fell to 95/85. His respirations slowed and he expired quietly on December 18, 1948.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case is most complicated and we shall certainly

not be able to discuss all of the interesting aspects involved. If the assumption is made that this long illness was a result of a single disease, it will be perhaps profitable to inquire what disease is compatible with such a clinical course. This patient was ill for four and one-half years and at times the disease process, if indeed it was a single one, involved the pleura, lymph nodes, liver, spleen and peritoneum. It seems likely that the tooth extraction and apparent secondary infection which occasioned his original admission were not of significance in relation to the clinical picture as a whole. It was of interest, however, that at the time of his first admission, splenomegaly and hepatomegaly were noted. At the time of the second admission a pleural effusion was present. Dr. Flance, can you suggest a disease which may have started with a pleural effusion and gone on to the clinical manifestations which were exhibited here?

DR. I. JEROME FLANCE: Pleural effusion, either inflammatory or malignant, associated with splenomegaly is compatible with a number of diseases which involve the reticulo-endothelial system. Included in that group are such infections as tuberculosis and histoplasmosis; among malignant diseases, certainly the lymphomas merit serious consideration.

DR. ALEXANDER: Would you seriously consider tuberculosis as the etiologic factor here?

DR. FLANCE: In retrospect, the fact that this patient was afebrile during most of his illness and the fact that except after nitrogen mustard and x-ray he had a normal blood count without monocytosis seem to me to exclude tuberculosis.

DR. ALEXANDER: Guinea pigs were inoculated with pleural and abdominal fluid from this patient on several occasions, and none of these animals died from tuberculosis. Would you comment on those results in relation to exclusion of tuberculosis as a possible diagnosis?

DR. FLANCE: I do not believe that a negative guinea pig inoculation completely excludes the diagnosis of tuberculosis, nor

do I think that the fact that no tubercles were found in microscopic sections from the involved areas excludes the diagnosis.

DR. ALEXANDER: But you would exclude the diagnosis on the basis that the patient was essentially afebrile with a normal blood count for most of the duration of his illness?

DR. FLANCE: Yes, I think that in this particular situation both of those findings are most important.

DR. ALEXANDER: Dr. Skilling, you saw this patient. Would you tell us what your thoughts were in regard to the possible diagnosis when the patient first consulted you?

DR. DAVID M. SKILLING: I saw him for the first time just before his second admission to this hospital. As was noted he had a bloody pleural effusion, and I was rather impressed by cells which strongly suggested Reed-Sternberg cells. However, in the absence of lymph node involvement I was loath to accept the diagnosis of Hodgkin's disease on the basis of cell block studies alone. No cells suggestive of any other malignant disease were observed. The negative guinea pig studies seemed to me to constitute strong evidence against a diagnosis of tuberculosis, and I agree with Dr. Flance that the absence of fever, likewise, was not consistent with a diagnosis of tuberculosis in this particular situation. I was unwilling to exclude that diagnosis completely, however, until I had followed him for many months.

DR. ALEXANDER: Is localized pleural effusion common in Hodgkin's disease?

DR. SKILLING: I have never seen it without evidence of hilar adenopathy or involvement of lymph nodes at some other site.

DR. ALEXANDER: What is your opinion on that subject, Dr. Reinhard?

DR. EDWARD H. REINHARD: I would agree with Dr. Skilling. Bloody pleural effusion is certainly not the rule in Hodgkin's disease although I suppose it may occur.

DR. BRUCE D. KENAMORE: Did this man have a tuberculin test?

DR. ALEXANDER: Yes, he had a negative tuberculin test. Dr. Moore, do you believe

that the patient may have had Hodgkin's disease:

DR. CARL V. MOORE: If we did not have the numerous negative biopsy reports and if we were not aware that this man failed to show any response to nitrogen mustard, I think that Hodgkin's disease would be an apt diagnosis. In view of these observations, however, I think one may discard the diagnosis of Hodgkin's disease.

DR. ALEXANDER: What disease would you suggest in its place?

DR. CARL MOORE: I am unable to offer a diagnosis. I think, as Dr. Flance pointed out, that one of the granulomas should be considered, but I cannot be specific.

DR. ALEXANDER: Dr. Reinhard, are you willing to discard the diagnosis of Hodgkin's disease? I believe you saw the lymph node sections.

DR. REINHARD: I saw at least one of them and did not think the microscopic picture suggested Hodgkin's disease. In addition there were a number of clinical features which would be most unusual in Hodgkin's disease. The patient never had fever except on rare occasions and he never had significant lymphadenopathy. Furthermore, there was no leukocytosis and no eosinophilia. I administered nitrogen mustard to this patient as a therapeutic test. We thought we were justified in so doing, in that had he had Hodgkin's disease we probably would have helped him. He made no response whatsoever and I agree that Hodgkin's disease does not seem to merit further consideration.

DR. ALEXANDER: Do patients with Hodgkin's disease always respond to nitrogen mustard therapy?

DR. REINHARD: Certainly in a great majority of patients there is a good response provided the patient has not received nitrogen mustard previously. The improvement may be of extremely brief duration, but pain and anorexia particularly are benefited. Fever, which so often accompanies Hodgkin's disease, is also usually controlled by nitrogen mustard therapy.

DR. ALEXANDER: May not a patient have Hodgkin's disease without exhibiting peripheral lymphadenopathy?

DR. REINHARD: That is possible, but unlikely. It seems to me that in a patient such as this man, in whom tuberculosis and Hodgkin's disease can be fairly well ruled out, one has to consider fungus infections seriously. I distinctly remember a patient presented at a conference here some years ago in whom at autopsy there was diffuse actinomycosis with abscesses in the spleen. The infection had extended up through the diaphragm and had given rise to a left pleural effusion. Such a sequence of events may have occurred here.

DR. HENRY A. SCHROEDER: There are certain features in this case which are not unlike those described in polyserositis. Usually, however, the pericardium is involved in polyserositis and there is certainly no evidence that such involvement was present here.

DR. ALEXANDER: To me, one of the most impressive features about this case was the adhesive peritonitis. Dr. Kenamore, what explanation do you have for this finding?

DR. KENAMORE: It seems to me that the most likely possibilities, namely, tuberculosis and carcinomatosis, have been excluded. I think it is fair to say that the latter has been fairly well excluded on the basis of the repeated biopsy specimens, cell blocks and exploration. Lymphoma may also give rise to this clinical picture.

DR. ALEXANDER: Dr. Scheff, what is your opinion?

DR. HAROLD SCHEFF: I would agree with Dr. Kenamore.

DR. ALEXANDER: Dr. Ackerman, you saw these biopsy sections when they were sent through the surgical pathology laboratory.

DR. LAUREN V. ACKERMAN: I was asked to review a section from this rather complicated case and I am afraid that I was not able to be of much help. I would agree that there was no evidence of tumor or of Hodgkin's disease, either in the lymph node or in the pleura. The findings were chiefly those of fibrosis. The section from the pleural fluid showed large numbers of what I interpreted as mesothelial cells; I could not convince myself that any of them

were true Reed-Sternberg cells. I have never found it possible to make a diagnosis of Hodgkin's disease on the basis of examination of cell blocks made from either pleural or peritoneal fluid. I have, however, in several instances made a diagnosis of lymphosarcoma. I think that the latter diagnosis is less difficult to make on cell block specimens. A section of the pleura taken at the time of thoracotomy showed a great deal of fibrous tissue and evidence of chronic inflammation. There were large cells present which remotely suggested Reed-Sternberg cells, but I am afraid that one could not identify them as such. Several of the sections taken at the time of the abdominal exploration were most interesting. I should like to point out some of the difficulties involved in attempting to make a definitive diagnosis from cell blocks of peritoneal fluid. Figure 1 is an example of proliferation of the peritoneum which occurred in a patient with cirrhosis of the liver. I suspected carcinoma when I saw this section and subsequently when the patient died he was found to have cirrhosis without carcinoma. Figure 2 is a section of a cell block of normal peritoneal fluid in which the pseudo-acini certainly suggest tumor. Mesothelial cells may be multinucleated and may even have mitotic figures. It may be most difficult to distinguish them from carcinoma cells.

DR. THOMAS H. HUNTER: Is it not possible that this patient had a mesothelioma?

DR. ACKERMAN: I do not believe that there is any way of ruling that diagnosis in or out.

DR. HUNTER: A patient with mesothelioma may have a very prolonged course as this man did. I saw a similar patient at the Presbyterian Hospital in New York who was a most baffling diagnostic problem for a rather long period of time. He, too, had involvement of both the pleural space and peritoneum.

DR. ALEXANDER: If this patient had had carcinomatosis which involved many of the abdominal viscera, would you not have expected that biopsy from an involved area would have shown the lesion?

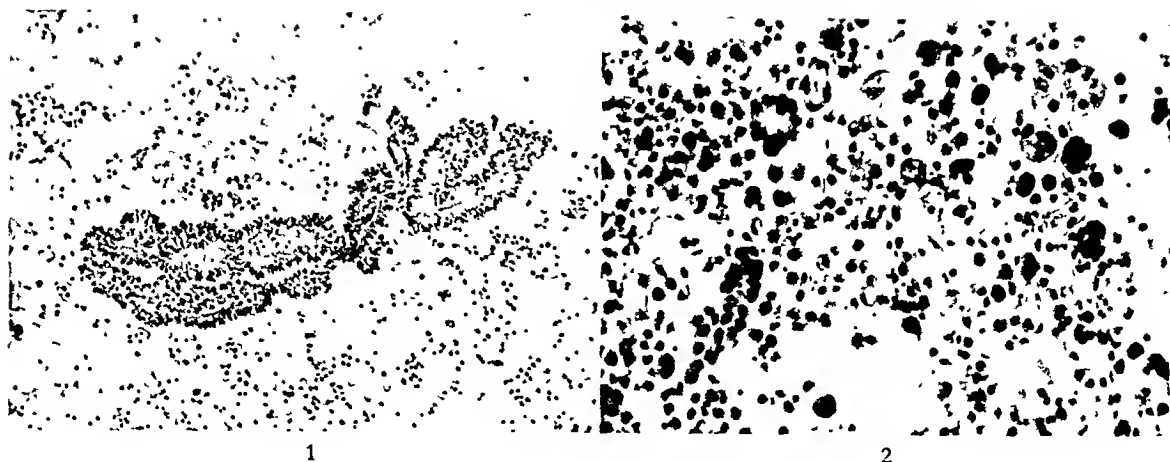


FIG. 1. Photomicrograph of a paraffin section made from peritoneal fluid; note the large pseudo-acini. This section was thought to be carcinoma by several pathologists. At postmortem examination the patient had cirrhosis of the liver; there was considerable peritoneal reaction with proliferation of mesothelial cells but no carcinoma.
 FIG. 2. Photomicrograph of paraffin section of normal peritoneal fluid; numerous pseudo-acini are present. Note the very large cells and the pleomorphism.

DR. ACKERMAN: When this patient was explored, the gross appearance did not suggest carcinomatosis to me nor did I find anything in the biopsy that suggested that diagnosis. At the time of operation carcinoma of the pancreas had been considered but such a clinical course as this man exhibited would be most unusual.

DR. REINHARD: It seems to me that the possibility of fungus infection still remains here.

DR. ALEXANDER: I should think that if this had been a fungus infection the causative organism would have been demonstrated sometime during the intensive study.

DR. SKILLING: At the time pleural fluid was originally removed from this man's chest a thorough search was made for fungi but none was found.

DR. ALEXANDER: In summary, I think that we would all agree that there is no obvious diagnosis in this case. It seems unlikely that either tuberculosis or carcinoma was responsible and Hodgkin's disease also seems unlikely. Fungus infection has been suggested but no evidence has been secured to substantiate it. Finally, mesothelioma has been proposed. I believe we shall have to depend on the pathologists to demonstrate the nature of the lesion which produced this most complicated and unusual clinical picture.

Clinical Diagnosis. ? Fungus infection of unknown type; ? mesothelioma.

PATHOLOGIC DISCUSSION

DR. CLARENCE PICKARD: The right pleural cavity contained 800 cc. of clear greenish-yellow fluid. There was a small focus of fibrin on the posterior surface of the right lung. The left pleural cavity (Fig. 3) was completely obliterated from apex to diaphragm by an extremely firm, dense mass of light tan fibrous tissue, varying from 2 to 60 mm. in thickness, which penetrated into the lung substance and was so firmly attached to the chest wall that it could not be stripped away. The lung within this hard shell was very firm to palpation. Aropy, mucopurulent secretion was present in the bronchi.

All the abdominal viscera were matted together by massive diffuse adhesions. The parietal peritoneum was 1 to 3 mm. thick and was studded with multiple, miliary, firm, gray nodules as much as 3 or 4 mm. in diameter. The visceral peritoneum and mesentery likewise were thickened and nodular. (Fig. 4.)

A small, firm, gray nodule, 2 cm. in diameter, was present in the body of the pancreas and extended into the posterior wall of the stomach. There was a large, soft, spongy mass lying anteriorly between

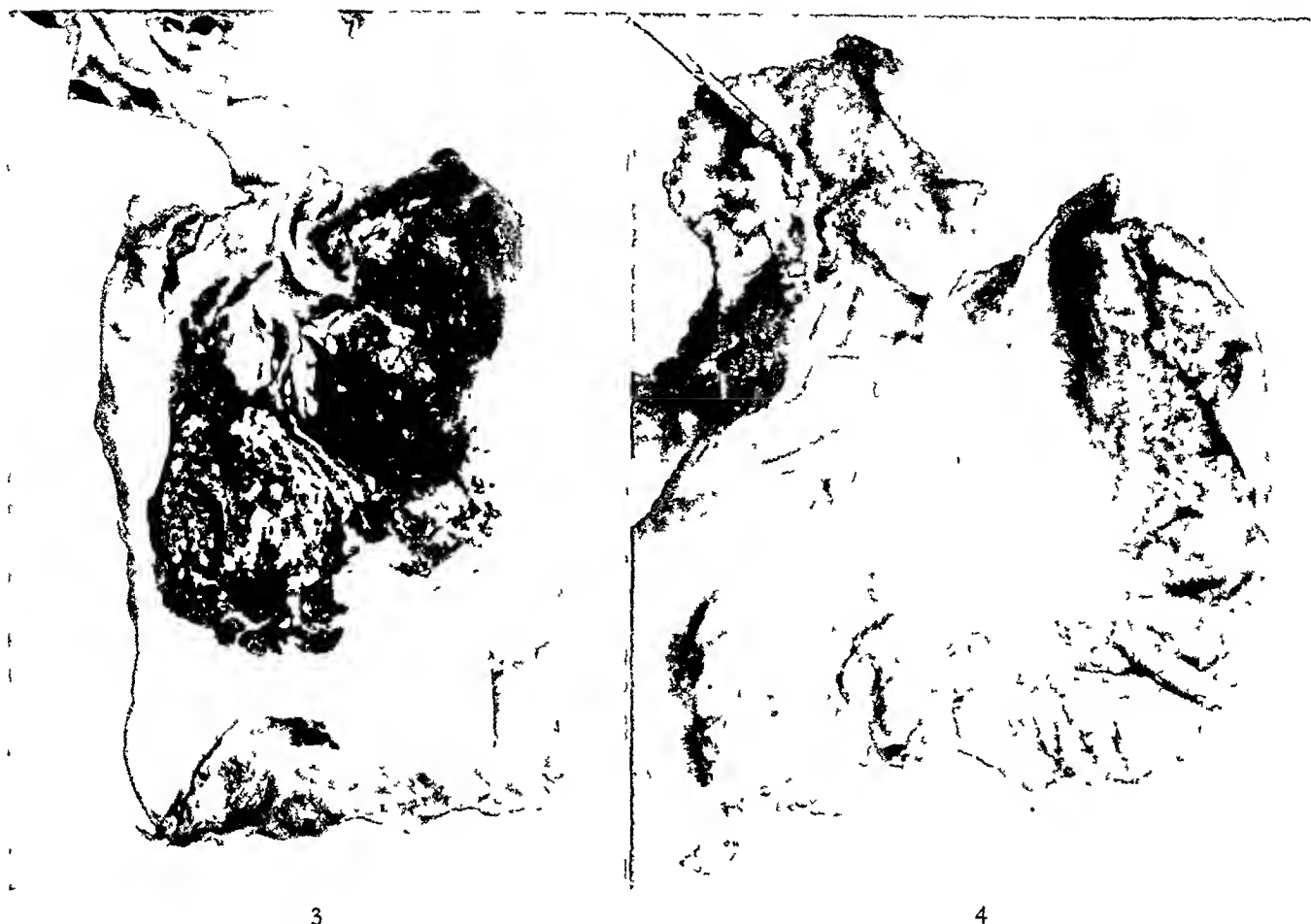


FIG. 3. Photograph of the pleura and lung showing the thickening of the pleura due to the mesothelioma. The underlying lung is collapsed.

FIG. 4. Massive thickening of the mesentery due to involvement by the mesothelioma.

the stomach and colon. All of these structures were firmly fixed together. The mucosa of the entire gastrointestinal tract was intact.

Other significant findings were generalized serous atrophy of fat and a small heart with brown flabby myocardium.

DR. ROBERT A. MOORE: The gross observations were not too helpful in establishing a diagnosis. In our preliminary examination we were impressed by the tumor mass in what appeared to be the substance of the pancreas, by the nodules over the surface of the peritoneum and by the apparent involvement of some of the lymph nodes about the head of the pancreas. These and the large mass in the upper abdomen were certainly suggestive of the diagnosis of carcinoma of the pancreas. Such a tumor is one of the more common intra-abdominal carcinomas producing widespread metastases to the peritoneum inasmuch as the pancreas itself is immedi-

ately adjacent to the peritoneum and cells apparently are shed into the peritoneal cavity and become implanted over its surface. The principal findings that were not in keeping with that diagnosis were the changes within the left pleural cavity which we interpreted at the time of the gross examination as chronic pleurisy with fibrous thickening of the pleura. We did not associate these two findings and consequently we made two separate diagnoses: carcinoma of the pancreas with metastases to the peritoneal cavity and to the regional lymph nodes, and fibrous thickening of the pleura and obliteration of the left pleural cavity.

One objection to the diagnosis of pancreatic carcinoma arose. Although it is quite possible for carcinoma of the pancreas to metastasize in the way it was presumed that this lesion did—that is, without metastases to the liver or to the thoracic cavity—it is not common. A second diag-

nostic possibility was therefore considered, namely, a tumor whose primary site was the peritoneal surface, the so-called mesothelioma; however, the mass in the substance of the pancreas appeared to be of such a character that we were led to believe that it probably represented the primary lesion. All of the other organs were carefully searched, particularly the lung, because carcinoma of the bronchus may lead to changes similar to those observed in the left pleural cavity. Many of the tumors described in the literature and accepted over a period of years as mesotheliomas of the pleura have been proved by more careful examination to be primary bronchogenic carcinomas which have spread into the pleural space. There was one specimen in point in the museum at Western Reserve University which for fifteen or twenty years was used as an example of mesothelioma of the pleura. One day Dr. Karsner was studying carcinoma of the bronchus and in the course of his investigation he opened several of the bronchi in that particular specimen which had not been previously opened. One of them was found to be the site of a classical primary carcinoma of the bronchus. It is therefore necessary to establish the diagnosis of mesothelioma on the basis of both positive and negative evidence. In other words, it must be shown that a tumor has not, so far as one can determine, arisen in some organ and then spread to involve the pleural or peritoneal surface. Second, the histologic characteristics of the tumor must be consistent with what one would expect if the tumor had originated from mesothelial cells.

The photomicrographs from the autopsy material illustrate the histologic character of the tumor in this case. Figure 5 is from a nodule in the peritoneal cavity which Dr. Pickard described. There are large polygonal or round cells that are oriented to one another, in that they are lined up in flat sheets. They do not form glandular spaces and many of the sheets of cells have a connective tissue core as if the tumor was

papillary in type. Papillary forms of mesotheliomas have been described both in the peritoneum and pleura. Figure 6 is another section at higher magnification. The cells have an abundant quantity of cytoplasm and large anaplastic nuclei with prominent nucleoli. In some sites the tumor forms sheets of cells with opposing surfaces flattened against the adjacent cells. Such an arrangement is one which is characteristic of a mesothelioma. At an even higher magnification (Fig. 7) the multinucleated character of some of the cells is apparent. Some of the multinucleated cells have overlapping nuclei such as are frequently seen in the Hodgkin's type of giant cell.

A differential histologic point in the diagnosis of mesothelioma is the absence of mucin within the cells. Not all carcinomas contain mucin in terms of gross or general microscopic appearance, but it is most unusual for a carcinoma originating from a mucin-secreting organ, such as bronchus, pancreas or the gastrointestinal tract, not to contain small globules of mucin in some cells. A stain for mucin in these preparations showed absolutely none in any of the cells.

In sections from the pleura the histologic picture was essentially similar. Figure 8 illustrates the dense connective tissue, which I suspect was related to the radiation therapy, and a buried mass of tumor which has undergone necrosis in its avascular center. Figure 9 is a higher magnification of a field in that nodule in which the cells, aside from vacuolation of the cytoplasm, show essentially the same characteristics as the malignant cells in the peritoneum. The last photograph (Fig. 10) is of a section of a tracheobronchial lymph node which was not recognized in the gross as containing tumor. In some of the sinusoids, however, are small groups of cells identical with those in the pleura and in the peritoneum.

In sections of the pancreas the lobules of parenchyma were distinctly separated from the nodules of tumor and there was no transition from normal cells to tumor cells as is characteristic of primary carcinomas

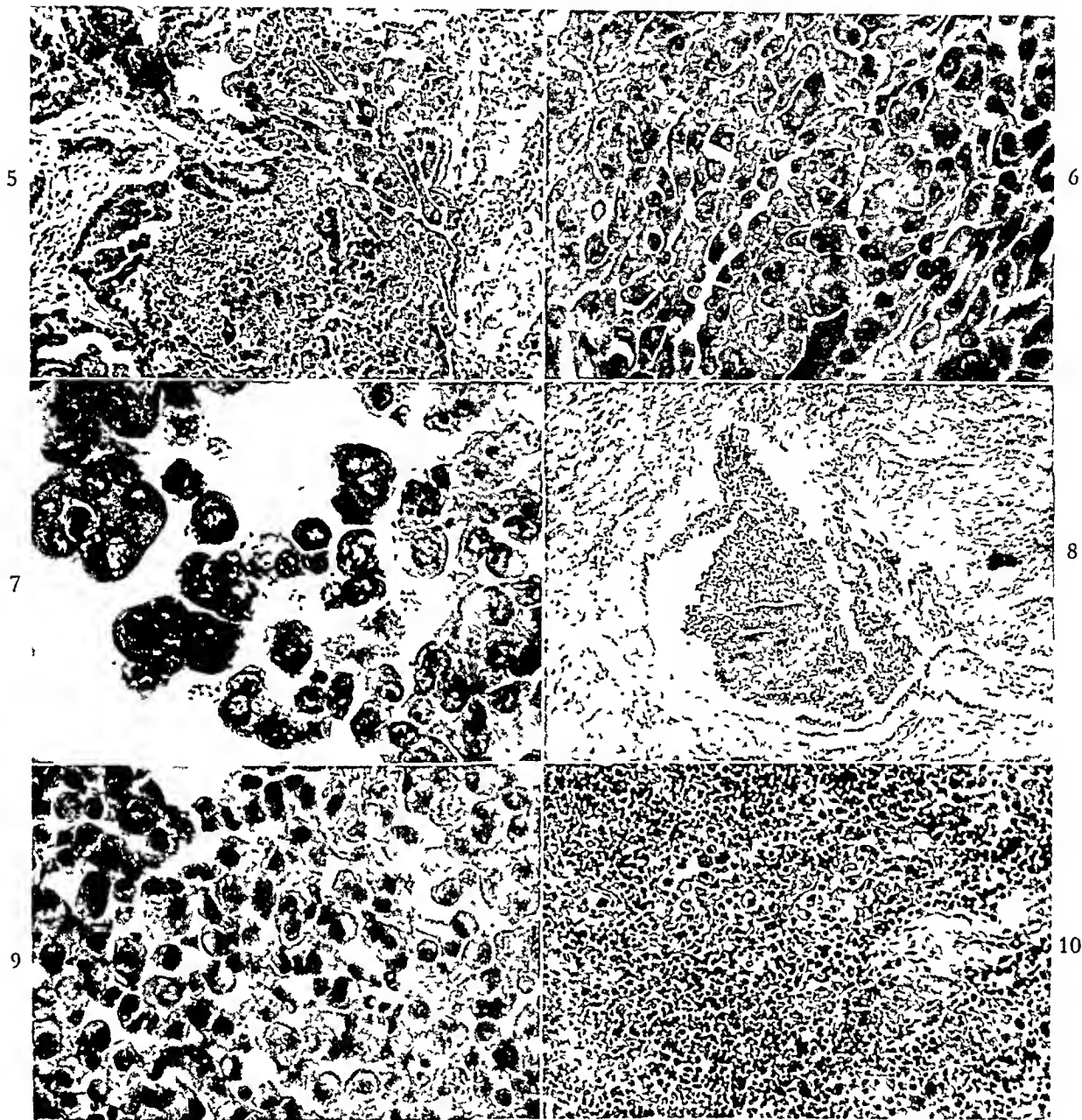


FIG. 5. Section of a peritoneal nodule in which the cells of the mesothelioma are arranged in a papillary pattern.

FIG. 6. A nodule of tumor from the peritoneum in which the mesothelioma is of a solid character.

FIG. 7. Multinucleation, large nucleoli, abundant cytoplasm and anaplastic nuclei in the cells of the peritoneal tumor.

FIG. 8. A nodule of partially necrotic mesothelioma buried in dense fibrous tissue from the left pleural cavity.

FIG. 9. Cellular details of the mesothelioma of the pleura which are essentially identical with the peritoneal tumor.

FIG. 10. Isolated metastatic cells of the mesothelioma in a tracheobronchial lymph node.

of that organ. By careful re-examination of the gross specimen we have also been convinced the tumor was not within but rather around the head of the pancreas.

From the microscopic study then there is evidence which enables us to come to a definitive diagnosis. First, the histologic characteristics of this tumor are those of a mesothelioma and second, the only alternate

possibility—that of a primary carcinoma—has been excluded by the absence of characteristic findings of pancreatic carcinoma. Therefore, the final diagnosis is mesothelioma involving both the peritoneal and pleural surfaces.

Dr. Hunter's comment about a case of mesothelioma involving two mesothelial surfaces was most informative; we had been

unable to find reference to such a case. I think a final and essentially unanswerable problem in this case is whether the tumor arose in the pleura and spread to the peritoneum, whether it was a primary tumor of the peritoneum which spread through the diaphragm to the left pleura or finally whether it was a tumor which arose simultaneously in two serous surfaces. The long clinical history is consistent with the general observation that these tumors do not grow very rapidly.

DR. ALEXANDER: Were you surprised that the diagnosis was not revealed when sections of the biopsies of the pleura and peritoneum were studied?

DR. ROBERT MOORE: No, I was not surprised; even at the time of autopsy the pleura was mostly dense fibrous tissue. In the section of pleura which we studied, for example, I demonstrated one nodule of tumor; in that same section there was one other nodule one-quarter the size of the first. That constituted the total amount of tumor in one section. The chance omission of tumor in a given biopsy specimen is obviously quite possible, particularly in a case such as this.

DR. ACKERMAN: When I was told the final diagnosis in this case, I reviewed the biopsy material with increased interest. I can say that the first biopsy of the pleura showed nothing but fibrosis. It is unfortunately true that unless a biopsy is taken from the right area it is very difficult to make a diagnosis of mesothelioma in the presence of minimal foci of proliferation of mesothelium. I think that it would have been perfectly possible to make the diagnosis here if the biopsy had been taken from a different area. The cell blocks of both the pleural fluid and peritoneal fluid undoubtedly contained tumor cells which we interpreted merely as stimulated or proliferating mesothelial cells.

DR. ROBERT MOORE: The point is this: in hindsight there are tumor cells in some of the material, but any pathologist who made the diagnosis of a mesothelioma on the basis of the biopsy material could not

have supported it. There were no cells not entirely consistent with hyperplasia of the peritoneal surface in response to the presence of a fluid over a long period of time.

DR. HUNTER: The patient I had in mind repeatedly accumulated blood-stained fluid in his pleural and abdominal cavities. There was one outstanding feature of that fluid: it was extremely viscous and had the consistency of cold honey. It was found to contain large amounts of hyaluronic acid. As a matter of fact it took about an hour to remove 2 or 3 hundred cc. of the fluid. Later hyaluronidase was injected directly into his peritoneal cavity and then the fluid was removed with ease.

DR. ACKERMAN: Dr. Hunter's observation is very interesting because these tumors are essentially similar to tumors which arise within the joints and which also produce large amounts of hyaluronic acid.¹ In regard to mesotheliomas several excellent papers may be consulted for further information.²⁻⁵

Final Anatomic Diagnoses. Mesothelioma involving the pleural surfaces of the left thoracic cavity with complete obliteration of the pleural space, and involving the peritoneum with extension into the pancreas, posterior wall of the stomach and wall of the transverse colon; metastatic mesothelioma in the left tracheobronchial and bronchopulmonary lymph nodes and in the mesenteric lymph nodes; atelectasis of the left lung, moderate.

Acknowledgment: The photographs were made by the Department of Illustration, Washington University School of Medicine, St. Louis, Mo.

¹ MEYER, K., SMYTH, E. and DAWSON, M. H. The isolation of a mucopolysaccharide from synovial fluid. *J. Biol. Chem.*, 128: 319, 1939.

² RHIND, J. A. and WRIGHT, C. J. E. Mesothelioma of the peritoneum: report of a case and review of the literature. *Brit. J. Surg.*, 36: 359, 1949.

³ WELLS, A. H. Papillomatosis peritonei. *Am. J. Path.*, 11: 1011, 1935.

⁴ YOSHIDA, T. Gleichzeitige Papillomatose der Pleura und des Peritoneums, zugleich ein Beitrag zur Frage des primären Carcinoma der serösen Häute. *Virchows Arch. f. path. Anat.*, 299: 363, 1937.

⁵ FISCHER-WASELS, B. Über die primären malignen Geschwülste der Serosadeckzellen. *Ztschr. f. Krebsforsch.*, 37: 21, 1932.

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE NATIONAL MEETING HELD IN ATLANTIC CITY
MAY 3, 1949

RENAL CLEARANCE OF CREATININE BY PATIENTS WITH MUSCULAR DISEASE. *Frank H. Tyler, M.D., Salt Lake City, Utah.* (From the Department of Medicine, University of Utah.)

In recent years it has become obvious as the result of a number of studies that the renal clearance of endogenous creatinine is a good measure of glomerular filtration rate in normal individuals and in most patients with nephritis. When this method was used to study the creatine-creatinine metabolism of patients with progressive muscular dystrophy, strikingly low filtration rates were found. When the standard inulin and p-aminohippurate clearances were measured, it was found that the glomerular filtration rate (Cl In), the renal plasma flow (Cl PAH) and the filtration fractions were normal. Simultaneous creatinine clearances, however, ranged from 30 to 70 per cent of the inulin clearance values. Furthermore, the reduction in creatinine clearance showed good correlation with the severity of muscular wasting. The same observation in a less striking degree was made in two patients who had hyperthyroidism with muscular atrophy.

The explanation of this apparent discrepancy is not clear. Three hypotheses suggest themselves: First, the creatinine may be found in the serum in some fashion in the presence of certain muscle disorders. Second, the renal handling of creatinine may be different in the dystrophic patient than in the normal. Third, use of the Jaffé reaction for determination of serum creatinine may have led to falsely high values for serum creatinine in the dystrophic patient as the result of some interfering chromogen in the blood serum.

STUDY OF URINARY COPROPORPHYRIN EXCRETION IN PATIENTS WITH NEOPLASTIC DISEASES. *Howard R. Bierman, M.D., D. Michael Crile, M.D., Louis Strait, Ph.D. and*

M. K. Hrenoff, B.S. San Francisco, Calif. (From the National Cancer Institute, National Institutes of Health, U. S. Public Health Service and the University of California Medical School.)

Over many months studies on patients without therapy have shown cyclic increases in coproporphyrin urinary excretion. Patients with various neoplastic diseases treated with nitrogen mustard have shown a pronounced coproporphyrinuria within one to three days after intravenous administration of methyl-bis(beta chloroethyl) amine. While the mechanism of coproporphyrin excretion was exhausted by repeated frequent doses of nitrogen mustard in one case, there appeared to be a stoichiometric relationship in some patients so that increased dosage of nitrogen mustard caused an increased coproporphyrin excretion within the ranges of 0.1 to 0.6 mg. per kg. body weight.

MECHANISM INVOLVED IN THE FAILURE TO RAISE THE WHITE BLOOD COUNT WITH TRANSFUSED LEUKOCYTES. *Austin S. Weisberger, M.D., Robert W. Heinle, M.D. and Richard Hannah, M.D. (by invitation) Cleveland, Ohio.* (From the Department of Medicine, Western Reserve University School of Medicine.)

Failure of blood transfusions to raise the leukocyte count is a common clinical observation. This was studied by transfusing concentrated suspensions of leukocytes and products of disintegrated leukocytes into rabbits. Leukocyte suspensions were obtained from the peritoneal cavity after distention with physiologic saline. These were concentrated by centrifugation, resuspended in Tyrode's solution and transfused into the veins or arteries of the same (autotransfusion) or other (heterotransfusion) rabbits. Leukocytes were disintegrated with su-

personic vibration, the material centrifuged and the supernatant fluid administered intravenously.

Autotransfusion of leukocytes resulted in sudden, profound leukopenia in fourteen of sixteen rabbits, the average time of onset was 2.8 minutes, average duration 2.2 hours and average decrease in leukocytes 69.3 per cent. Initial leukocytosis never occurred but in nine rabbits subsequent significant leukocytosis developed after an average of 4.3 hours.

Heterotransfusion of leukocytes in seventeen rabbits and administration of cell-free aqueous extracts of disintegrated leukocytes to ten rabbits resulted in a sudden profound leukopenia in every instance similar in all details to the results just described. Subsequent leukocytosis occurred in more than one-half of the animals.

Leukopenia was associated with the appearance of large numbers of cells in the lungs. This was conclusively demonstrated by using leukocytes labeled with radioactive phosphorus. Removal of cells previously circulating and the occurrence of leukopenia after administration of particle-free extracts indicate that this is more than simple filtration of foreign particles. It is evident that leukocytes contain a substance(s) capable of affecting the number of circulating cells. Preliminary experiments indicate that thromboplastin and histamine are not responsible for the effects observed.

ACQUIRED HEMOLYTIC ANEMIA: RELATION OF AMOUNT OF ERYTHROCYTE ANTIBODY TO ACTIVITY OF THE DISEASE. *Robert S. Evans, M.D. San Francisco, Calif.* (From the Department of Medicine, Stanford University School of Medicine.)

An antibody-like agent can be demonstrated on erythrocytes of patients with acquired hemolytic anemia with the Coombs reagent (anti-human globulin rabbit serum), but the observation that abnormal sensitization persists during complete remissions throws doubt on the importance of the antibody as a primary cause of the disease. However, studies in eleven patients with acquired hemolytic anemia indicate a direct correlation between the amount of antibody on the erythrocyte and activity of the disease. The adsorbed antibody is assayed by the susceptibility of the washed erythrocytes to agglutination in serial dilutions of a standard Coombs reagent. It can be shown by analogy with the Rh hyperimmune antibody that the

concentration of Coombs reagent necessary to produce agglutination is inversely proportional to the amount of antibody on the cell surface.

The erythrocytes of patients with acquired hemolytic anemia have been agglutinated by dilutions of the Coombs reagent varying from 1 to 2 to 1 to 1,280. The cells of eight patients with active disease before or after splenectomy were agglutinated by high dilutions (1 to 80 to 1 to 1,280) whereas the red cells of seven patients in remission following splenectomy (five) or spontaneous (two) with normal pigment excretion were agglutinated only in dilutions of 1 to 2 to 1 to 80. Two patients studied before and after splenectomy exhibited a sharp reduction in the amount of adsorbed antibody associated with cessation of rapid hemolysis. Spontaneous remission in two patients was observed to follow more gradual reduction of the amount of antibody on the cell surface.

The data suggest that a critical concentration of antibody on the cell is necessary to produce accelerated destruction and that subcritical sensitization is compatible with normal longevity of erythrocytes as measured by normal pigment excretion. Splenectomy, when it is effective, acts by reducing the amount of antibody below the critical level, probably by removal of a certain proportion of the antibody-producing tissue.

CLINICAL AND METABOLIC EFFECTS OF DIFFERENT NUTRIENTS IN PATIENTS WITH CIRRHOSIS. *Gordon R. Morey, M.D. (by invitation), Camen R. Paynter, M.D. (by invitation), C. Frank Consolazio, M.D. (by invitation), Mary A. Maloney, M.D. (by invitation), Louis J. Vorhaus, M.D. (by invitation), Mildred Breimyer (by invitation) and Robert M. Kark, M.D. Chicago, Ill.*

Clinical and metabolic observations were made to compare four different types of medical therapy in each of four patients with cirrhosis. The control regimen included a fixed daily intake of calories (twice basal requirement); protein (2.5 Gm./Kg. body weight); fat (30 per cent of total calories); carbohydrate (total calories less calories from protein and fat); salt (0.9 Gm. NaCl) and water (2.5 L.). The 126-day study consisted of seven consecutive eighteen-day metabolic periods. Throughout this time the patients consumed the control diet which was supplemented daily as follows during the

second, fourth and sixth eighteen-day periods: (1) 120 Gm. of salt-poor, 10 per cent amino acid solution, given intravenously; (2) choline, cystine, methionine and B complex vitamins given orally and liver extract given intravenously; (3) salt-poor human serum albumin given intravenously plus the nutrients mentioned in the second category.

The health of all patients improved during the study, as manifested by weight gain without fluid retention, decrease in number and size of vascular spiders, reduction in ascites and edema and in two patients by diminution of the liver size. The only significant change among seven serial liver function tests was in serum cholinesterase activity which correlated closely with clinical variations.

Positive nitrogen balances were observed in all patients throughout the study but were greatest during therapy with intravenous amino acids and with human serum albumin. The urinary excretion of calcium increased during the periods of (1) amino acid therapy and (2) supplementation by lipotropic substances, vitamins and parenteral liver. When sulfaguanidine was given for one day to three patients with diarrhea, a transient sharp rise in urinary calcium excretion was observed, with an increase in one patient up to 1 Gm. per day from a previous value of 0.45 Gm.

PATHOLOGIC AND FUNCTIONAL CHANGES IN THE LIVER FOLLOWING UPPER ABDOMINAL OPERATIONS. *Norman Zamcheck, M.D., Thomas C. Chalmers, M.D. and Charles S. Davidson, M.D. Boston, Mass.* (From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

The effects of major surgery on the liver were studied in fifteen patients before and after sixteen operations, including twelve subtotal gastrectomies, three cholecystectomies and one exploratory laparotomy. Serial liver function tests, including bromsulphalein retention (twelve patients), serum bilirubin concentration (six patients) and thymol turbidity and flocculation (six patients) were performed before and after operation. Specimens of the liver were obtained by biopsy from six patients immediately after the abdomen was opened. In fifteen patients,

including these six, tissue was obtained at the completion of the operation just before the abdomen was closed.

The tissue obtained at the end of the operation in every patient showed pathologic evidence of acute inflammation of the liver. The lesions were primarily of three types: (1) capsular and subcapsular inflammation; (2) focal collection of neutrophilic polymorphonuclear cells distributed largely around the central vein of the lobule, the portal area being spared in most instances; (3) necrosis of liver cells. In none of the control biopsies obtained at the beginning of the operation were these pathologic changes found. The bromsulphalein retention increased in every instance postoperatively and remained elevated for a variable number of days. Serum bilirubin was increased to above normal in three patients postoperatively. No significant change in thymol turbidity or flocculation occurred.

It is concluded that performance of these major surgical procedures upon the upper abdomen was followed by morphologic and functional evidence of liver impairment. The changes observed appeared to be directly related to the operations rather than to coexistent lesions of the stomach or gallbladder.

STUDIES IN PROTEIN METABOLISM WITH THE AID OF S^{35} -LABELED-METHIONINE. *Laurance W. Kinsell, M.D., Sheldon Margen, M.D., Harold Tarver, M.D., Julie McB. Frantz, M.D., Erin K. Flannagan, M.D., Vernon T. Thompson, U.S.N. and Robert V. Deal, U.S.N. San Francisco, Calif.* (From the Division of Medicine, University of California Medical School, the Metabolic Research Unit, U. S. Naval Hospital—University of California, Division of Biochemistry, University of California, and the Department of Chemistry, Mills College.)

S^{35} -labeled-methionine has been administered to normal males and to patients with (1) chronic liver damage, (2) idiopathic hypoproteinemia and (3) Cushing's syndrome. Incorporation of the labeled material in plasma protein, as well as its excretion in urine and stool, have been quantitated.

From these studies it has been found that incorporation of the S^{35} in plasma protein goes

on more slowly with chronic liver damage than in the normal controls, that its rate of disappearance from plasma protein occurs about at the same rate as in normal individuals and that the S^{35} of urinary sulfate is in accord with these findings. In the patient with idiopathic hypoproteinemia the initial rate of incorporation in plasma protein occurs much more rapidly than in the normal control, after which the rate of disappearance from plasma protein occurs proportionately even more rapidly, with the result that within three weeks this patient is in a net deficit as compared to the control. Again the S^{35} content of urinary sulfate is in agreement with these findings. In the patient with Cushing's syndrome (who was studied only over a three-day period immediately preceding removal of an adrenocortical tumor) the initial rate of incorporation of the S^{35} in plasma protein was significantly more rapid than in the normal control.

From these data one may conclude that S^{35} -labeled-methionine is a valuable tool for quantitation of protein anabolism and catabolism.

A METHOD OF EVALUATING TISSUE PROTEIN STORES. *John E. Harroun, M.D., Stanley Levey, Ph.D. and Charley J. Smyth, M.D. Eloise, Mich.* (From the Wayne County General Hospital.)

Total circulating proteins and fractions were determined before and thirty minutes after infusion of 1 L. of physiologic saline (at a rate of approximately 20 ml. per minute). Total circulating hemoglobin was determined in several cases. Plasma volumes were measured before and after the infusion using the dye method (T-1824). Sixteen patients, varying in nutritional status from normal to severe malnutrition, were studied. After the initial observations four malnourished subjects were placed upon a high caloric (3,000 to 4,500), high protein (2.5 to 5.0 Gm./Kg./day) diet and studied through the transition from undernutrition to the normal nutritional state. Clinical criteria as to weight gain, subjective symptoms and reversal of abnormal liver function tests were used as guides to the re-establishment of normal nutrition.

The response to the infusion exhibited by patients in normal nutrition was constant and was characterized by an increase in plasma volume of about 400 ml., an increase in total

circulating protein of approximately 10 Gm. per square meter body surface and an increase in total circulating hemoglobin in those patients in whom this determination was made. The response exhibited by the malnourished patients also was constant but differed from the normal in that the plasma volume increased about 260 ml., whereas the total circulating protein decreased 10 or more Gm. per square meter of body surface. Total circulating albumin, although not constant in either group, tended to be increased in the presence of normal nutrition and tended to be decreased in undernutrition.

The pattern exhibited by subjects with normal nutrition is interpreted as evidence of adequate labile tissue protein stores. Failure of total circulating proteins to increase after infusion in the malnourished subjects is interpreted as a manifestation of depleted tissue protein stores. That this is the probable mechanism is strengthened by a demonstration of reversal of response from that characterizing malnutrition to that of normal nutrition during the course of a high caloric, high protein diet in four patients so studied.

SERIAL BIOPSY STUDIES IN CIRRHOSIS OF THE LIVER. *W. D. Davis, Jr., M.D. New Orleans, La.* (From the Ochsner Clinic.)

Studies of the clinical course and response to therapy in twenty-nine patients with cirrhosis of the liver by means of serial liver biopsies as well as the usual laboratory procedures have resulted in reasonable agreement between microscopic and other laboratory findings and the clinical courses of the patients.

In ten patients with clinical manifestations of hepatic decompensation there was microscopic evidence of advanced fibrosis with varying degrees of hepatic cellular necrosis, fatty change, leukocytic infiltration and regeneration of the bile ducts. Of these the only patients who made significant progress under therapy were numbered among the five in whom there were definite fatty changes in the liver. Explanation of this is believed to lie in the fact that hepatic cells, rendered temporarily useless by the presence of large amounts of fat, may regain their function quickly as the fat is mobilized and thus furnish a reservoir of hepatic function which may be utilized by proper therapy. Disappearance of cellular infiltration and edema may contribute in small degree to this effect.

In the compensated group the presence or absence of fatty change seemed to make little difference in the clinical progress which was uniformly good in the patients who followed the therapeutic regimen. These patients frequently improved despite use of low caloric diets with adequate proteins and vitamin supplements. In general they presented less severe degrees of fibrosis, cellular necrosis and regeneration of bile ducts than the decompensated group although there were in many instances leukocytic infiltration and fatty changes.

Diminution in fat could be detected as soon as ten days after the institution of therapy. Cellular infiltration disappeared more slowly whereas in those patients who improved parenchymal hepatic necrosis rapidly disappeared. Diminution in fibrosis was not evident.

Methionine was considered of value particularly in three patients who exhibited rapid diminution in fatty infiltration of the hepatic cells despite a grossly inadequate caloric and protein intake during the period of observation. There was no evidence that methionine was of particular value in those patients who were able to maintain adequate oral alimentation.

EVIDENCE THAT RENAL SODIUM EXCRETION IS CONTROLLED BY ADRENAL CORTICAL ACTIVITY AND INGESTED SODIUM MAY DISPLACE INTRACELLULAR POTASSIUM IN NORMAL SUBJECTS. *Alexander Leaf, M.D. and L. H. Newburgh, M.D. (Introduced by Sibley W. Hoobler, M.D.) Ann Arbor, Mich. (From the Department of Internal Medicine, The Medical School, University of Michigan.)*

The effects of great variation in sodium intake were studied in normal subjects maintained on fixed diets of adequate calories and protein with very low sodium and chloride content. At definite periods additional sodium was administered either as the chloride or citrate.

Salt restriction resulted in reduction in urinary sodium and chloride to minute amounts accompanied by increase in urinary nitrogen, urea, uric acid, potassium and phosphorus. Administration of sodium chloride or citrate caused high urine sodium with decrease in urine uric acid, potassium, phosphorus, blood and urine urea and positive nitrogen balance. The drop in blood urea was not accounted for by alteration in glomerular filtration rate but

was explained by a decrease in the rate of protein catabolism. A strongly positive potassium balance occurred simultaneously with the high sodium excretion that could not be accounted for by decreased protein catabolism.

All these changes are explained by alterations in adrenal cortical activity. The need to conserve body sodium was met by increased activity of the desoxycorticosterone-like hormone. An associated increase in protein-catabolic hormone activity was elicited also. Sodium administration abolished the need to conserve sodium and thus depressed adrenal cortical activity. This not only allowed a large urinary sodium excretion but also gave evidence of a marked decrease in activity of protein-catabolic hormone.

In all subjects sodium citrate administration initially caused a marked positive sodium balance. The degree of alkalosis was reduced by entry of large amounts of sodium into the cells with displacement of large amounts of potassium as evidenced by the strongly negative potassium balance.

CEREBRAL BLOOD FLOW IN VASCULAR DISEASE OF THE BRAIN, WITH OBSERVATIONS ON EFFECTS OF STELLATE GANGLION BLOCK AND NICOTINIC ACID. *Peritz Scheinberg, M.D. (Introduced by E. C. Kunkle, M.D.) Durham, N. C. (From the Department of Medicine, Duke University School of Medicine.)*

Since the nitrous oxide method for cerebral blood flow, devised by Kety and Schmidt, measures blood flow per unit weight of brain, normal values are obtained regardless of variations in brain size as long as cell function is normal. If the arterial inflow to the normal brain is reduced without affecting cellular function, the arteriovenous O_2 difference widens and O_2 consumption is normal. If cellular metabolism is decreased, arteriovenous O_2 difference is narrowed and O_2 consumption lowered.

This technic, modified by drawing continuous samples of arterial and internal jugular venous blood rather than five separate arterial and venous samples, was used to determine cerebral blood flow in fifteen patients. All patients had hypertensive vascular disease except one who had mitral stenosis with repeated cerebral embolisms. The subjects fell into two groups: (1) those with changes in their mental status

and (2) those without alteration in their mental status but who had papilledema and retinopathy from hypertension.

The patients in the first group showed reductions in cerebral blood flow and only slight increases in arteriovenous O_2 difference, with resulting lowered O_2 consumption. Normal values were obtained in the second group. The decreased cerebral blood flow in the first group probably resulted from increased resistance offered by diseased cerebral vessels. The decreased O_2 consumption cannot be explained by the reduced blood flow alone because other studies show that a chronic reduction in cerebral blood flow can be completely compensated by widened arteriovenous O_2 difference. The decreased O_2 consumption is therefore indicative of cellular dysfunction produced by varying degrees of ischemia.

Unilateral procaine stellate blocks were done on sixteen subjects, including normals and patients with cerebral vascular disease. The blocks caused no significant changes in cerebral blood flow, O_2 utilization or cerebrovascular resistance.

Intravenous nicotinic acid in patients with vascular disease likewise produced no change.

CONSIDERATIONS OF RENAL, HEPATIC AND EXTREMITAL ARTERIOVENOUS DIFFERENCES IN CONCENTRATION OF RADIOMERCURY OF A MERCURIAL DIURETIC. *Pervis Milnor, M.D., George Burch, M.D., Thorpe Ray, M.D., Sam Threefoot, M.D. and Gerald Berenson, M.D. New Orleans, La.* (From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana.)

Certain aspects of the pharmacodynamics of the mercury in a mercurial diuretic labeled with radiomercury have been studied in seven subjects; in five patients renal venous catheterization was performed and in the other two hepatic venous catheterization. Four subjects were normal, two had chronic congestive heart failure and one had only a right kidney. Samples of arterial blood, extremital and renal or hepatic venous blood, as well as samples of urine obtained by ureteral or vesical catheterization were collected simultaneously.

In general, differences in the arteriovenous concentration varied from 5 to 25 per cent, with considerable fluctuation during the

initial ten minutes. Thereafter there was a slight but steady decrease in these differences, during which time they were directly proportional to the arterial concentration of the tracer. Differences in concentration between arterial and extremital venous blood were greater than those between either arterial and renal or arterial and hepatic venous blood during the initial five minutes after injection. After ten or twenty minutes no constant differences existed between arterial and extremital venous concentrations. A difference of about 10 per cent in arteriohepatic venous concentration occurred in one normal subject; no constant difference could be detected in the patient with severe chronic congestive heart failure.

The peak of urinary excretion occurred ten to twenty minutes later than the peak of the arteriovenous differences. Urinary excretion varied independently of percentage renal extraction or arterial concentration. Urinary concentration of radiomercury and rate of urinary flow varied discordantly, but each of these functions for two kidneys of the same subjects varied concordantly.

The data indicate a retention of mercury by the kidney, at least during the initial twenty to thirty minutes. An early antidiuretic effect of mercury was noted.

ELECTROCARDIOGRAPHIC CONTROL OF CORONARY VENOUS CATHETERIZATION IN DOGS AND MAN, AND SIMULTANEOUS MEASUREMENT OF CORONARY BLOOD FLOW, CARDIAC WORK AND EFFICIENCY. *Walter T. Goodale, M.D., Harold D. Levine, M.D., Richard J. Bing, M.D. and Donald B. Hackel, M.D.* (From the Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass., the Physiology Section, Medical Division, Army Chemical Center, Md. and the Department of Surgery, Johns Hopkins University and Hospital, Baltimore, Md.)

Coronary venous catheterization has proven feasible under fluoroscopic visualization in eight of eleven recent attempts in man and in 98 per cent of one hundred dogs. Alternate postero-anterior and right anterior oblique views provided the stereoscopic effect necessary to identify pertinent landmarks associated with the coronary sinus and cardiac veins. With a specially

designed catheter, blood was easily withdrawn from coronary veins without evidence of significantly obstructing coronary venous return. Withdrawal of very dark desaturated blood and observance of mean pressures only 2.3 mm. higher than right auricular pressure with a characteristic pressure pattern helped to confirm successful insertion. Final confirmation and more precise localization of the catheter tip was obtained from the electrocardiographic complexes obtained from a catheter tip lead, compared with a simultaneous limb lead. Complexes were obtained in the great cardiac vein, coronary sinus, posterior left ventricular vein and middle cardiac vein which were characteristic of each location, and were readily distinguishable from tracings with the tip in the right auricle or ventricle.

Adaptation of the cerebral flow method of Kety and Schmidt has permitted calculation of coronary blood flow simultaneously with coronary arteriovenous oxygen difference and cardiac work measured from the product of cardiac output and systemic blood pressure. Left ventricular efficiency in man, calculated from these observations in five normal patients, was 17 per cent ($0 = \pm 7\%$). Duplicate or triplicate normal coronary blood flows showed a maximum spread of 18 per cent and a mean value of 87 cc./100 Gm. of left ventricle/min. Myocardial oxygen consumption was 11 to 21 cc./100/Gm./min., relatively constant in each subject.

Coronary venous catheterization appeared innocuous and less hazardous than catheterization of the right ventricle or pulmonary artery.

RELATIONSHIP OF QUINIDINE BLOOD LEVELS TO THERAPY OF CARDIAC ARRHYTHMIAS.
Maurice Sokolow, M.D. and Archie L. Edgar, M.D. San Francisco, Calif. (From the Medical School, University of California.)

The quantitative aspects of quinidine therapy were investigated by determining multiple blood and urine concentrations (using the photofluorometric extraction method of Brodie, as modified by Lilienthal) during conversion of auricular fibrillation and flutter to sinus rhythm. The inverse relationship between rising blood levels and falling auricular rates found during therapy indicated the relationship between blood quinidine levels and the cardiac effects of the drug. Sinus rhythm was re-established in twenty-four of twenty-eight therapeutic at-

tempts (85 per cent conversion). The average peak blood level at the time of conversion was 6.3 mg./L. Seventy-five per cent of the patients were converted with levels between 4 and 8 mg./L. In only three patients was the level required for conversion less than 4 mg./L. The amount of quinidine required for conversion (resulting in peak levels greater than 4 mg./L.) was usually 0.4 or 0.6 Gm. given every two hours for five doses. In the four patients who failed to convert levels of between 7 and 13.7 mg./L. were obtained. The maximum concentration following a given dose of quinidine was reached in two to three hours and by four hours the blood level had begun to fall. The increment in blood level obtained by successive identical doses became progressively smaller so after four or five doses to increase further the blood level larger individual doses were required. The rapidity of the rise of blood quinidine was much greater when a two-hour schedule was used as compared to a four-hour schedule.

There were eight relapses with four reconversions. Reconversion in the other four was not attempted. Maintenance dose schedules ranged from 0.2 Gm. three times a day to 0.4 Gm. six times a day. Inadequate mid-day peaks were obtained with less than 0.4 Gm. three times a day; therefore, adequate maintenance doses of quinidine should probably be at least 0.4 Gm. four times a day.

The data presented emphasize a more rational method of quinidine therapy for both conversion of arrhythmias and for maintenance of sinus rhythm.

EFFECT OF ABDOMINAL COMPRESSION ON CHLORIDE EXCRETION FOLLOWING ADMINISTRATION OF HYPERTONIC SALINE SOLUTION. *W. H. Cargill, M.D., W. B. Fackler, M.D., R. L. McWhorter, Jr., M.D. and J. V. Warren, M.D. Atlanta, Ga. (From the Departments of Physiology and Medicine, Emory University School of Medicine and the Medical Service, Lawson VA Hospital.)*

It is generally agreed that edema formation in congestive heart failure is associated with a reduction of renal blood flow and glomerular filtration rate. Whether salt retention is due to these changes alone or to extrarenal factors has been the subject of much controversy. The present studies have been undertaken in an

attempt to elucidate further the mechanisms of the altered salt excretion in congestive failure.

The renal blood flow, glomerular filtration rate and chloride excretion have been studied before and after rapid intravenous administration of 250 cc. of 4 per cent saline solution in a group of ten subjects. In addition to studies in the basal state observations were made during a period of increased abdominal pressure produced by an abdominal binder inflated to a pressure of 80 to 100 mm. Hg. In normal subjects without abdominal compression the saline solution produced an immediate increase in the chloride excretion. With the abdominal binder inflated, however, there was no increase in chloride excretion following the saline injection. The saline injection in itself did not significantly alter the renal blood flow or glomerular filtration rate, but abdominal compression usually resulted in a considerable diminution in blood flow and filtration rate. Increased abdominal pressure alone produced a fall in the basal rate of chloride excretion. Results similar to those in normal subjects were obtained in a patient with diabetes insipidus indicating that activity of the posterior lobe of the pituitary gland was not responsible for these changes.

These experiments demonstrate that increased intra-abdominal pressure results in a failure normally to excrete injected sodium chloride solution. The situation so produced is in many ways similar to that seen in congestive heart failure.

USE OF OXYGEN CONSUMPTION DURING EXERCISE AS A QUANTITATIVE MEASURE OF CARDIAC RESERVE. *Kenneth Chesky, M.D. and Herbert S. Sise, M.D. Boston, Mass.* (From the First and Third Medical Services, Boston City Hospital and the Department of Medicine, Tufts Medical School.)

The purpose of this study was to devise a simple test as a quantitative measure of cardiac function based on oxygen consumption during exercise. It was found that normal subjects increase the oxygen consumption in linear fashion with increasing increments of exercise while cardiac patients showed either (1) a low fixed or "maximal" oxygen consumption during increasing increments of exercise, (2) oxygen consumptions which were subnormal for work loads of moderate intensity but which were not

fixed, (3) oxygen consumptions which resembled normal individuals.

The patients were exercised on a bicycle ergometer at three speeds with a standard brake tension. Oxygen consumptions were determined with a standard Benedict-Roth basal metabolism machine. The slope of the tracing was checked by two maximal inspiratory efforts before and after the second minute of exercise. Normals for these grades of exercise consisted of 346 ± 57 , 564 ± 77 and 690 ± 81 cc of oxygen per square meter of body surface. It was found that the clinical degree of incapacity of thirty-two patients corresponded well with the degree of limitation of oxygen consumed during either the greatest of the three exercises or the greatest exercise that the patient could tolerate. Most ambulatory cardiacs, with the exception of patients with severe mitral stenosis, could tolerate all three degrees of exercise. In three patients with myocardial disease the oxygen consumption for a given grade of exercise was increased from 360 to 467, 387 to 517 and 477 to 622 cc./minutes/square meter of body surface thirty minutes after administration of 1.6 mg. of cedilanid intravenously. One case of unsuspected failure was picked up by this test and the response to digitalis. In two patients with mitral stenosis the oxygen consumption with the given degrees of exercise fell from 595 to 546 in one, and insignificantly in another from 700 to 690 cc./minutes/square meter of body surface thirty minutes after cedilanid. Withdrawal of digitalis has been associated with a fall in maximum oxygen consumption of 467 to 315 cc./minutes/square meter of body surface in a patient with hypertensive disease. There was no change in a patient with valvular disease upon withdrawal of digitalis.

In the experience of the authors this is a valuable and simple clinical test of cardiac function.

HEMODYNAMIC EFFECTS OF HYPOTENSIVE AGENTS IN MAN. *Edward D. Fries, M.D., Joseph R. Stanton, M.D., Julius Litter, M.D., James W. Culbertson, M.D., Meyer H. Halperin, M.D., F. Corbin Moister, M.D. and Robert W. Wilkins, M.D. Boston, Mass.*

In order to clarify the mode of action of drugs used in the treatment of essential hypertension the hemodynamic effects of four drugs, each

representative of a class of hypotensive agents, were studied: sodium nitrite (direct-acting peripheral vasodilator), dihydroergocornine (sympatholytic agent), sodium amytal (sedative) and veratrum viride (reflex, neurogenic vasodilator). These were compared as to their effects on cardiac output (Fick), mean arterial pressure, total peripheral resistance, muscle and hepatic-portal blood flows, renal clearances and sympathetic vasopressor reflexes in man.

Drugs which influence central nervous system vascular centers (veratrum, dihydroergocornine) lowered total peripheral resistance without reduction in cardiac output or compensatory tachycardia. Peripheral vasodilators (sodium nitrite) lowered both cardiac output and pulmonary arterial pressure with compensatory tachycardia. The response to amytal was variable and in subhypnotic doses the drug was seldom hypotensive. Following all drugs the muscles usually exhibited greater vasodilatation than the hepatic-portal area while the renal vasculature manifested an autonomy of tone characterized by an initial reduction in BF and GFR followed by a quick return to control values regardless of continuing hypotension. Dihydroergocornine and other sympatholytic agents inhibited vasoconstrictor reflexes but exhibited variable hypotensive responses whereas veratrum, which also acts through the nervous system, did not inhibit sympathetic vasoconstrictor nerves but produced hypotension more uniformly.

These results suggest that following hypotensive drugs (1) the autonomy of the kidney vasculature prevents prolonged alteration of renal hemodynamics, (2) vasodilatation occurs with greater frequency in muscles than in the hepatic-portal area. Following drugs which act through central nervous system vascular centers an integrated hypotensive response occurs. In addition the studies with veratrum suggest that nerves other than sympathetic vasoconstrictors should be considered in regard to the neurogenic regulation of arterial pressure.

RELATIONSHIP BETWEEN SERUM ANTI-DIURETIC SUBSTANCES AND URINARY CORTICOSTEROID IN THE HUMAN. *Charles W. Lloyd, M.D. and Julia Lobotsky, M.S. Syracuse, N. Y.* (From the Syracuse University College of Medicine.)

A relationship between adrenal cortical steroids and the posterior pituitary anti-

diuretic hormone has been postulated (Silvette and Britten). Birnic, Eversole and Gaunt have recently devised a method for measuring in rat serum antidiuretic substances which may be of posterior pituitary origin. In our laboratory the method of Daughaday, Jaffe and Williams for estimation of freely water-soluble adrenal cortical steroids has been modified to permit measurement of poorly water-soluble steroids. A study of the relationship in the human between serum antidiuretic activity, urinary corticosteroid, volume and chloride has been made.

Blood for assay of antidiuretic activity was drawn at the completion of a twenty-four-hour urine collection period. Measurements of the twenty-four-hour corticosteroid and chloride excretion were made. A relative increase of the antidiuretic substance in the ratio

$$\frac{\text{serum antidiuretic substance}}{\text{urinary corticosteroid}}$$

is associated with water retention and a relative increase of the urinary corticosteroid is associated with diuresis. During the crisis in Addison's disease a preponderance of antidiuretic activity with low corticosteroid excretion is found. The increase in corticosteroid excretion following treatment with desoxycorticosterone is associated with a decrease in serum antidiuretic substance. In diabetes insipidus a relatively or absolutely low value of antidiuretic material is present. The cirrhotic who retains water has a preponderance of antidiuretic activity; when diuresis occurs, the corticosteroid level may be very high and the serum may contain no antidiuretic material. In premenstrual water retention a preponderance of antidiuretic activity is found.

ADRENOCORTICAL HYPERACTIVITY IN ACROMEGALY WITH SEVERE DIABETES: HORMONAL AND CLINICAL REMISSION AFTER TREATMENT. *William H. Daughaday, M.D. and Cyril M. MacBryde, M.D. St. Louis, Mo.* (From the Department of Internal Medicine of Washington University Medical School.)

Clinical, biochemical and hormonal studies have been made on a male patient, aged thirty-eight, with acromegaly associated with severe diabetes and insulin resistance. When first observed, only impaired glucose tolerance with-

out clinical diabetes was present. Severe diabetes appeared six months later with great suddenness. Control of the diabetes required a daily dose of insulin from 250 to 500 units over a period of about one year. He was treated with irradiation to the pituitary, stilbestrol and later methyl testosterone. While receiving methyl testosterone a remission occurred so that glycosuria became minimal even without insulin treatment.

We have attempted to elucidate the mechanism of insulin resistance in this patient by biochemical and hormonal studies. During the phase of severe diabetes there was severe lipemia and hypercholesterolemia. Upon subsidence of the diabetes the blood fats and cholesterol almost returned to normal. An attempt was made to demonstrate a factor in the patient's serum inhibiting peripheral utilization of glucose. However, the patient's serum did not inhibit the uptake of glucose by the isolated rat diaphragm.

During the active period of diabetes there was an elevation in the excretion of urinary "cortin" as measured by the liberation of formaldehyde from steroid residues. Values obtained were 1.9, 3.5, 2.4, 4.8 mg. per day (normal, circa 0.75 to 2.0 mg.). Excretion of 17-ketosteroids was a high normal with values from 16 to 36 mg. per day. Following clinical remission cortin excretion fell to 0.81, 0.85, 1.1 mg. per day and the 17-ketosteroids were also reduced to 4.5, 4.7 and 5.4 mg. per day.

The insulin resistance here described is probably hormonal in type and can be partly explained by adrenal cortical hyperfunction. An additional direct pituitary diabetogenic factor was not demonstrated but is presumed also to have been active.

EXPERIMENTAL EVIDENCE ON THE MECHANISM OF DIABETIC KETOSIS. *Lawrence E. Hinkle, Jr., M.D., George A. Conger, M.D. and Stewart Wolf, M.D. New York, N. Y.* (From the New York Hospital and the Departments of Medicine and Psychiatry of Cornell University Medical College.)

In a study of twenty-five human subjects with diabetes mellitus approximately fifty instances of clinical ketosis were observed to occur in a setting of emotional conflict and in the absence of other pertinent factors including infection. Moreover, day to day observation of these subjects both in and out of the hospital yielded a

close correlation between life situations, emotion and the metabolic state as reflected by glycosuria, ketonuria, insulin requirement and the symptoms of diabetes.

In an experimental study of nine of the subjects quantitative measurements of blood ketone and glucose concentrations and concomitant determination of urine volume and glucose were made before, during and after an interview in which intense emotional conflict was engendered. Ages of the patients varied from fourteen to sixty years and insulin requirements from 0 to 100 units per day. The chemical determinations were made on either peripheral venous blood or on blood withdrawn directly from a catheter introduced into the hepatic vein. In all cases a significant elevation of blood ketones, as well as a marked increase in the urine volume and rate of urinary glucose excretion, occurred during the traumatic interview. In the most severe diabetics the rapidity and degree of the increase in blood ketones and urine sugar was greatest, but nevertheless a marked degree of ketosis was produced in one of the mildest diabetics when the traumatic conflict situation was prolonged. The level of the blood glucose also fluctuated significantly and was usually lower at the end than at the beginning of the experimental period.

Thus significant emotional conflict has been shown to be associated with a rise in the blood ketone level and a simultaneous "washing out" of glucose through diuresis. The evidence indicates that such a mechanism is commonly involved in the decompensation of diabetes and the production of clinical ketosis.

EFFECT OF ADMINISTRATION OF POTASSIUM BASED ON STUDY OF THE HUMAN SUBJECT AND THE DOG. *Samuel Bellet, M.D., William A. Steiger, M.D., P. C. Gazes, M.D. and Carl S. Nadler, M.D. Philadelphia, Pa.* (From the Divisions of Cardiology and Chemistry, Philadelphia General Hospital and the Robinette Foundation, University of Pennsylvania.)

Potassium is frequently administered to patients who have varying degrees of hypopotassemia. The problem of determining the maximum therapeutic and early toxic action is of considerable importance. Its chemical estimation, while highly desirable, is not always available initially or during the various phases

of its administration. This problem was studied during the intravenous injection of 200 to 1,500 cc. of an isotonic solution of potassium chloride over a period of one to six hours in sixty human subjects, the ages of whom ranged from twenty to eighty years, for the following indications: During the hypopotassemic phase following treatment of diabetic acidosis, following fluid loss due to intestinal obstruction and other causes, inanition, diarrhea and other conditions. During administration of potassium these patients were studied clinically, by continuous electrocardiographic tracings and frequent estimation of the serum levels of this electrolyte. The results of these studies have indicated that the electrocardiogram is valuable in following potassium effects and gives early evidence of its toxic action. The range of safety is apparently considerable. Since potassium produces its toxic effect chiefly on the heart and because this electrolyte is administered to patients with varying degrees of myocardial damage which could conceivably alter the toxic dose, a study was performed on normal dogs and dogs with myocardial infarction. The evidence of the initial and varying stages of its toxic effects were noted in the electrocardiogram and correlated with the level of the serum potassium. It was found that the tolerance of dogs with mild degrees of myocardial infarction did not vary much from the normal. In dogs with moderate to severe grades of myocardial infarction there was a definite diminution in tolerance to potassium. The determination of the initial toxic effect by serial electrocardiograms taken during administration of potassium is of help in determining the dose to be given since the cardiac changes in this stage are reversible.

SIGNIFICANCE OF ELECTROLYTE ABNORMALITIES IN MANAGEMENT OF ANURIA, OLIGURIA AND EDEMA. *Charles L. Fox, Jr., M.D. New York, N. Y.* (From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University.)

Anuria, oliguria and edema are associated with significant abnormalities in the electrolyte concentrations of both plasma and urine. When similar changes are produced experimentally in man and animals, marked impairment of renal function follows.

Observations were made in ten patients with anuria or oliguria resulting in rapid elevation of their blood urea nitrogen. Three patients had also developed edema and ascites. In all instances plasma sodium and bicarbonate were reduced and chlorides relatively elevated. In the urine the concentration of sodium was low and the chlorides exceeded the sodium; potassium was variable.

Hypertonic (1 molar) sodium lactate or acetate was administered orally to six patients in sufficient amounts to adjust their plasma electrolytes toward normal. Plasma volume expanded as gauged by hematocrit measurements (presumably as water was withdrawn from cells previously subjected to the hypotonic extracellular fluid); repeated doses of sodium salts were required before the plasma sodium and bicarbonate reached normal. The urinary output increased gradually and diuresis with reduction in blood urea nitrogen occurred in these patients after the plasma sodium and bicarbonate had approached normal. Repeated measurements of distribution of radioactive sodium and changes in both body weight and edema were correlated with readjustment of the plasma to isotonicity and excretion of more water than sodium.

The data indicate clearly that attainment of normal tonicity and volume of the plasma are of primary importance for restoration of renal function.

EVALUATION OF PANCREATIC FUNCTION BY MEANS OF INDUCED HYPER-AMYLASEMIA FOLLOWING MORPHINE AND SECRETIN. *W. J. Snape, M.D., C. W. Wirts, M.D. and M. H. Friedman, Ph.D. Philadelphia, Pa.* (From the Departments of Medicine and Physiology, Jefferson Medical College and Hospital.)

An attempt was made to evaluate pancreatic function by means of an injection of morphine and secretin in forty-four subjects, including twenty-five control patients, eight patients with cancer of the pancreas, six with pancreatitis and five with cancer of the stomach. A fasting blood sample was taken to determine the basal serum amylase; 10 to 15 mg. of morphine sulfate was given subcutaneously and 1 unit of secretin per Kg. was injected intravenously thirty minutes later. Blood samples were taken at fifteen,

thirty, sixty and ninety minutes thereafter for serum amylase determination.

In the twenty-five control patients the average basal value was 133.5 units; following an injection of secretin the peak value occurred at the end of the thirty or sixty-minute interval, with an average value of 389.3 units. In the patients with cancer of the pancreas pre- and post-stimulation and peak values were significantly lower than in the control patients. In 62.5 per cent of these patients amylase values were below the lowest obtained in the control patients before stimulation and after stimulation 50 to 75 per cent had values lower than the minimal control figure. In the other two pathologic groups there was little difference from the control subjects. In three of the six patients with pancreatitis, pain identical with the clinical attack was produced following injection of secretin.

Animal experimentation has shown that injection of secretin after obstruction of the pancreatic ducts results in a transitory rise of the serum enzymes of pancreatic origin. This phenomenon depends on the presence of actively secreting acinar tissue because elevation of the blood enzymes does not occur after the gland atrophies. We achieved obstruction of the pancreatic duct by means of morphine and stimulation of acinar activity by secretin. On the basis of the lower values obtained in patients with cancer of the pancreas we may assume there is a decrease in functioning acinar tissue and therefore believe this procedure may have diagnostic value.

ACTION OF ACETYL-BETA-METHYLCHOLINE CHLORIDE (MECHOLYL) ON THE HUMAN COLON. *Fred Kern, Jr., M.D., Frank K. Abbot, M.D. and Thomas P. Almy, M.D. New York, N. Y.* (From the Department of Medicine, New York Hospital and Cornell University Medical College.)

In a physiologic study of patients with functional bowel disease two types of alteration in motility of the sigmoid were noted. Motility is increased in individuals with constipation and diminished in individuals with diarrhea. To elucidate the mechanism of these motility patterns we examined the effects of certain drugs influencing the autonomic nervous system. Mecholyl (acetyl-beta-methylcholine chloride), an agent which is known to produce diarrhea, was found by White and Jones to reproduce

many of the symptoms and proctoscopic signs of mucous colitis. We studied this drug intensively by means of kymographic recordings of pressure changes in an in-lying sigmoid balloon or by continuous proctoscopic observations of the rectosigmoid.

Mecholyl has been administered subcutaneously in amounts ranging from 2.5 to 10.0 mg. to twenty subjects. In fifteen of forty experiments marked diminution of wave-like motility in the sigmoid colon accompanied the usually observed effects of this drug. When these effects disappeared, the previous pattern of motility was resumed. In no instance did mecholyl produce augmentation of motility. When the rectosigmoid was observed proctoscopically in four normal subjects, mecholyl produced no significant changes in color or contractility. The aforementioned effects of mecholyl were blocked by atropine. In a patient with a transverse colostomy motility tracings were obtained from the cecum, splenic flexure and sigmoid. Mecholyl caused a marked increase of cecal activity, moderate stimulation of the transverse colon and cessation of motility of the sigmoid.

Thus mecholyl appears to stimulate the right colon and inhibit wave-like activity of the sigmoid, effects which enhance the evacuation of intestinal contents. It is inferred that the mechanism of emptying the bowel may be entirely a cholinergic phenomenon. It is of interest that most patients with functional diarrhea or ulcerative colitis spontaneously exhibit a similar diminution of wave-like motility of the sigmoid.

USE OF MAXTED'S ENZYME METHOD FOR GROUPING BETA-HEMOLYTIC STREPTOCOCCI. *Lewis W. Wannamaker, M.D., Floyd Denny, M.D., William R. Brink, M.D. and Edward Custer, M.D.* (Introduced by C. H. Rammelkamp, M.D.) (From the Streptococcal Disease Laboratory, Fort Francis E. Warren, Wyoming and the Department of Preventive Medicine, Western Reserve University, Cleveland, Ohio.)

During the course of a field study of streptococcal diseases at Ft. Francis E. Warren, Wyo., 692 strains of beta-hemolytic streptococci were isolated, of which 551 strains were grown from the throats of hospitalized respiratory patients and the remaining 141 strains were obtained

from routine cultures of normal soldiers. All 692 strains were successfully lysed by Maxted's enzyme which is produced by a strain of *Streptomyces albus*. A loopful of growth from a blood agar plate was inoculated into 0.25 cc. of the enzyme preparation and the mixture was placed in a water bath at 50°C. for two to twenty-four hours. After complete clearing had occurred the lysate was used as an antigen for grouping with rabbit antisera. Using the capillary tube technic, all 692 strains gave definite precipitin reactions with one of the more common groups. 672 strains (97 per cent) were found to be group A, two were group B, eleven were group C and seven were group G. Formamide extracts prepared by the method of Fuller were set up in parallel on the first 341 strains. In no case was there disagreement in the two methods. Groupings were checked on an additional seventy-nine strains by preparing hot acid extracts which were set up against group specific antisera. These results were also in complete agreement with those obtained by the enzyme method. It is suggested that Maxted's enzyme offers an efficient, rapid method for identifying group A beta-hemolytic streptococci.

PRIMARY SUTURE OF THE DIVIDED TRACHEA.

Bernard Maisel, M.D. and James A. Dingwall, M.D. New York, N. Y. (From the Department of Surgery, New York Hospital and Cornell University Medical College.)

Primary anastomosis of the cervical trachea following a cut throat injury was successfully carried out by one of us approximately two years ago. This was done without tracheotomy or drainage of the adjacent soft tissues. Stimulated by this an experimental study was undertaken in order to determine the physiologic processes of healing attendant on surgical repair of the trachea as representative of a cartilaginous organ.

In this preliminary study a small series of dogs was used. In one group, after exposure of the trachea through a midline neck incision, the trachea was completely divided and then immediately sutured employing continuous everting mattress sutures. Leaks were tested by submerging the joined segments in saline. In a second series complete segments measuring up to 2½ cm. in length were removed and the continuity of the trachea was re-established as

described. These animals were then observed by endoscopic examination, and specimens were removed at intervals of from one to six weeks for microscopic study. In all instances healing occurred or successful, leak-proof union was maintained by what is recognized surgically as primary union. No leaks occurred giving rise to subcutaneous crepitus or infection, and adequate airways were maintained without any appreciable stricture formation.

Although few, there are reports in the literature suggesting the feasibility of direct tracheal anastomosis. Recently Daniel gathered excellent evidence to show the remarkable autoregenerative ability of tracheal tissue about temporary prostheses, and Longmire reported the repair of an old post-traumatic defect by the temporary use of a lucite tube to bridge a gap in the cervical trachea. We believe that primary anastomosis of the trachea and bronchi may be entirely feasible in humans not only in repairing traumatic injuries but in resections of pulmonary and esophageal lesions where invasion of the air tube would seem to limit operability.

EFFECT OF AUREOMYCIN ON THE SURVIVAL OF VIRUS IN LYMPHOGRANULOMATOUS BUBOES. *John W. Runyan, M.D., Lisbeth M. Kraft, M.D. (by invitation) and Irving Gordon, M.D. Albany, N. Y.* (From the Department of Medicine, Albany Medical College, and the Division of Laboratories and Research, New York State Department of Health.)

Viruses of the lymphogranuloma venereum-pittacosis group frequently induce a carrier state. Since aureomycin has proved effective in the treatment of both clinical and experimental lymphogranuloma venereum, we wished to learn whether the virus persists in buboes during clinical improvement. Two patients were studied. Oral treatment with 24.5 and 19.5 Gm. of aureomycin for nine and ten days, respectively, resulted in high serum aureomycin levels and definite regression in the size of the buboes by the fourth day. Three weeks after treatment commenced the buboes had disappeared.

To detect the virus, bubo aspirates were inoculated intracerebrally in mice and into the yolk sacs of embryonated hens' eggs. The virus was isolated from each patient in the first five consecutive attempts: three times prior to

therapy and on the first and second days of treatment. Attempts at isolation were unsuccessful on the fourth and seventh days of treatment.

While the data do not permit decision as to whether subinfective quantities of virus still survived in the healed lymph nodes, the results indicate that infectivity does not persist for long following treatment. This is consonant with the rapid disappearance of the buboes.

CLINICAL EXPERIENCE WITH THE 4-AMINO DERIVATIVES OF PTEROYLGLUTAMIC ACID AND 2,6-DIAMINOPURINE IN THE TREATMENT OF NEOPLASTIC DISEASE. *J. H. Burchenal, M.D., D. A. Karnofsky, M.D., C. M. Southam, M.D., W. P. L. Myers, M.D., L. F. Carver, M.D., H. W. Dargeon, Jr., M.D., C. P. Rhoads, M.D. New York, N. Y.* (From the Sloan-Kettering Institute and Memorial Hospital.)

A total of eighty-two patients have been treated with various derivatives of pteroylglutamic acid characterized by the substitution of an amino group in the 4 position of the pteridine ring. Among these patients were thirty-four acute leukemias, fifteen chronic leukemias, ten lymphosarcomas, seven Hodgkins' disease, three osteogenic sarcomas, two Ewing's tumors, two neuroblastomas, two mycosis fungoides, two carcinomas of the lung and one each of the stomach and bladder, one fibrosarcoma, one multiple myeloma and one eosinophilic granuloma.

With the 4-amino derivatives of pteroylglutamic acid, toxic symptoms of stomatitis, diarrhea, gastrointestinal bleeding and loss of hair were occasionally seen. With 2,6-diaminopurine the most troublesome toxic symptoms were severe nausea and vomiting which often made adequate dosage impossible. Both types of drugs when pushed to toxic levels caused leukopenia and definite depression of the bone marrow.

Complete although temporary clinical remission in acute leukemia with reversion of the bone marrow to approximately normal was seen in four of twenty children, and one of fourteen adults treated with the 4-amino derivatives of pteroylglutamic acid. A second remission has thus far been induced by further therapy in all patients who relapsed following the first remission. In lymphosarcoma and eosinophilic granuloma in children and chronic myelocytic

leukemia in adults temporary clinical remissions occurred occasionally after therapy with the 4-amino derivatives. In lymphomas and other forms of neoplastic disease in adults no useful therapeutic results were noted.

EXPERIMENTAL EVIDENCE ON RELATIVE EFFECTS OF LIFE STRESS AND INHALED POLLEN IN HAY FEVER. *Thomas H. Holmes, M.D., Theodore F. Treuting, M.D. and Harold G. Wolff, M.D. New York, N. Y.* (From the New York Hospital and the Departments of Medicine and Psychiatry, Cornell University Medical College.)

An experimental attempt was made to clarify the relative importance of distressing life situations and inhaled pollens in the pathogenesis of hay fever. In thirty subjects, fifteen of whom had had hay fever, repeated quantitative studies of nasal function were made under uniform conditions in a room in which a known concentration of pollen was circulated. Nasal hyperfunction characterized by varying degrees of hyperemia, swelling and hypersecretion of the membranes as well as eosinophilia in the nasal secretions and circulating blood occurred in all subjects, "sensitive" or "normal," exposed to mixed ragweed pollen when the circumstances were appropriate.

When nasal function was average, neither sensitive nor normal subjects reacted to mixed ragweed pollen with sufficient evidence of nasal hyperfunction to produce symptoms. However, when there was pre-existing nasal hyperfunction from whatever cause, both groups reacted to the pollen with marked hyperfunction, weeping and sneezing. Thus during difficult life situations productive of conflict typical hay fever attacks followed pollen inhalation. Conversely, it was possible during pollen inhalation in the absence of frank hay fever to induce an attack by a discussion of significant personal problems and to induce subsidence of the attack by reassurance while the pollen is still being inhaled.

Unilateral procaine block of the stellate ganglion in ten subjects yielded evidence that nasal hyperfunction engendered by conflict situations was mediated through parasympathetic fibers in the greater superficial petrosal nerve. Inhalation of pollen following this procedure precipitated the signs and symptoms of unilateral rhinitis which spared the non-hyperfunctioning membrane on the uninjected

side. It was concluded that sensitive individuals differ from normals only in degree, that pollen or distressing life situations may induce nasal hyperfunction in either with associated local and circulating eosinophilia and symptoms of rhinitis. The various factors provocative of nasal hyperfunction with symptoms of hay fever thus exert an additive effect.

ERYTHROPOIETIC ACTIVITY OF EXTRINSIC FACTOR ON PARENTERAL ADMINISTRATION IN PERNICIOUS ANEMIA. *Frank H. Gardner, M.D., John W. Harris, M.D. and William B. Castle, M.D. Boston, Mass.*

According to Castle, interaction between the food (extrinsic) factor and the gastric (intrinsic) factor is required for the formation of the anti-pernicious anemia principle of liver—here considered to be vitamin B₁₂. The complete reaction does not occur *in vitro*. We have shown recently that the erythropoietic effect of orally administered vitamin B₁₂ is enhanced by the simultaneous administration of the gastric (intrinsic) factor although not to the extent observed when the same amount of vitamin B₁₂ is given alone parenterally.

In the present observations a daily dose derived from 400 Gm. of beef muscle was employed in the form of an autoclaved, 70 per cent alcohol filtrate of an aqueous extract of beef muscle from which the alcohol had been removed by free evaporation. In three patients with untreated pernicious anemia the preparation was inert upon daily oral administration, was moderately active when orally administered daily together with 150 cc. of normal human gastric juice and still more active upon intravenous administration without gastric juice. Microbiologic assays and erythropoietic effects indicate the presence of somewhat less than 1 microgram of vitamin B₁₂ in each daily dose of the beef muscle extract.

Comparisons of blood glucose and tyrosine levels following oral administration of these substances simultaneously with 150 cc. of normal human gastric juice or an equal amount of salt solution upon alternate days indicate no non-specific effect upon absorption attributable to the gastric (intrinsic) factor. This suggests the possibility that the food (extrinsic) factor is identical with or chemically closely related to vitamin B₁₂ and that the gastric (intrinsic) factor is essential merely for facilitation of

absorption of low concentrations of vitamin B₁₂ present in certain foods other than, for example, liver.

RELATIONSHIP BETWEEN ELECTROCARDIOGRAPHIC EVIDENCE OF RIGHT VENTRICULAR HYPERTROPHY AND PULMONARY ARTERIAL PRESSURE IN CHRONIC PULMONARY DISEASE. *John B. Johnson, M.D. (by invitation), John R. West, M.D., M. Irénée Ferrer, M.D., H. M. Weiner, M.D. and André Cournaud, M.D. New York, N. Y. (From the Bellevue Hospital.)*

This paper presents a group of thirty-eight patients with chronic pulmonary disease in whom studies of the pulmonary arterial pressure at rest and electrocardiographic evidence of right ventricular hypertrophy were made. The purpose of the study was to determine whether any correlation exists between pulmonary arterial pressures and electrocardiographic signs of right ventricular hypertrophy. The patients were studied by the right heart catheterization technic. The electrocardiographic study included measurements of the R/S ratio and the intrinsicoid deflections in the unipolar precordial V leads.

The patients were divided into three groups. Group I included nine patients with normal pulmonary arterial mean pressures at rest (15 mm. Hg or less) but whose mean pressures were elevated with exercise. Group II included sixteen patients with elevated pulmonary arterial mean pressures ranging from 16 to 30 mm. Hg. Group III included twelve patients with resting pulmonary arterial mean pressures above 30 mm. Hg. The electrocardiograms in group I showed no evidence of right ventricular hypertrophy. Group II, which included those with marked chronic pulmonary emphysema, fibrosis or both, also showed no specific electrocardiographic evidence of right ventricular hypertrophy although one patient showed an incomplete right bundle branch block. Nine of the twelve patients in group III showed specific electrocardiographic signs of right ventricular hypertrophy of incomplete right bundle branch block. One patient showed presumptive evidence of right ventricular hypertrophy. A high incidence of incomplete right bundle branch block (14 per cent) was found in thirty-seven patients.

The data suggest that most patients with chronic pulmonary disease whose resting pul-

monary arterial mean pressures exceed 30 mm. Hg will have right ventricular hypertrophy as indicated by the unipolar precordial V leads of the electrocardiograms. With lesser degrees of pulmonary arterial hypertension in this small series of patients, the electrocardiograms were of no value in the detection of right ventricular hypertrophy.

EFFECT OF LYSOZYME ON GASTRIC AND COLONIC MUCUS OF MAN *in Vitro*. *George B. Jerzy Glass, M.D. and Betty L. Pugh, M.D. (Introduced by Stewart Wolf, M.D.) New York, N. Y.* (From the Departments of Medicine and Psychiatry of the New York Hospital and of the Cornell University Medical College.)

Meyer and others have demonstrated that in human subjects with peptic ulcer and ulcerative colitis a significant increase occurs in the concentration of the mucolytic enzyme lysozyme in the gastric juice and stools, respectively. In view of the possibility that lysozyme acts to destroy the natural mucus coating of the stomach and bowel it seemed pertinent to explore *in vitro* the effect of lysozyme on human gastric and colonic mucus.

Tests for lysozyme activity were carried out by the viscosimetric method of Meyer, by volumetric measurement and by chemical analysis of products of mucus digestion. Purified egg white lysozyme and human tears containing approximately 500 units of lysozyme per cc. were used. The gastric mucus was obtained from normal subjects, achlorhydric subjects and from a fistulous human subject with a completely occluded esophagus. His gastric juice was thus free from contamination from saliva and nasorespiratory mucus. The colonic mucus was obtained directly from three fistulous human subjects with exposed evaginated segments of bowel.

Both the gastric and colonic mucus were tested in their native state at various pH values and after liquefaction by incubation or solution in dilute alkali. The mucus was also fractionated by the method of Glass and Boyd into its components, dissolved mucoprotein elaborated by the mucus cells of the gastric glands and visible mucus and mucoproteose derived from the lining columnar epithelial cells. No mucolytic action was displayed *in vitro* by lysozyme on human gastric or colonic mucus. Neither whole mucus

in its various preparations at various pH values nor any of the fractions of mucus from the stomach or colon were measurably changed by egg white or human lysozyme in tears. In the stomach another mucolytic enzyme was detected which was neither lysozyme nor pepsin. Contact of lysozyme with gastric mucus neither impaired nor enhanced the activity of the lysozyme on its mucinous bacterial substrate.

These observations lead to the inference that whatever the consequences of increased lysozyme secretion in ulcerative colitis they do not include digestion of the protective mucus coating of the stomach or colon.

METABOLISM OF HUMAN SERUM ALBUMIN IN MAN. *Richard D. Eckhardt, M.D. and Charles S. Davidson, M.D. Boston, Mass.* (From the Thorndike Memorial Laboratory, Second and Fourth Medical Services, Harvard, Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

The metabolic fate of albumin was investigated by comparing the effects of its administration orally as whole protein and intravenously as whole and as completely hydrolyzed protein. Two normal and three undernourished subjects, maintained on constant 50 Gm. protein diets, received 50 or 75 Gm. of whole or hydrolyzed albumin daily for six days during six metabolic studies of from three to five weeks' duration.

The following results were obtained: (1) Hydrolyzed albumin given intravenously was promptly metabolized. Urinary nitrogen excretion increased immediately and remained constant throughout albumin administration and returned to the fore-control value the day it was discontinued. (2) During and after administration of whole albumin orally a three to five-day lag occurred before the urinary nitrogen excretion and nitrogen balance became constant. (3) When whole albumin was injected intravenously, the metabolism required approximately two weeks for completion as evidenced by the slow disappearance of albumin from the blood and delayed and gradual excretion in the urine as non-protein nitrogen. (4) The rate of disappearance of intravenously administered whole albumin from the blood was similar in normal and undernourished subjects. (5) Undernourished patients burned less administered whole albumin, whether given by mouth or by vein,

than did normals. (6) Most efficient utilization of albumin followed its administration intravenously as a whole protein.

It is concluded that albumin is available to both normal and undernourished subjects for metabolism regardless of its form or route of administration. The delay of approximately two weeks in reaching nitrogen balance when whole albumin is given intravenously reflects its slow degradation while the less marked delay following oral administration depends upon the time required to complete digestion and absorption. Nitrogen balance is promptly achieved when hydrolyzed albumin is administered intravenously since the processes of digestion and absorption or of degradation have been circumvented.

SODIUM AND POTASSIUM EXCRETION IN PATIENTS WITH RENAL INSUFFICIENCY. *Belton A. Burrows, M.D., Robert R. Commons, M.D. and Charles H. Burnett, M.D. (by invitation) Boston, Mass. (From the Evans Memorial Hospital.)*

The relationship between urine volume and sodium and potassium excretion has been studied under conditions in which changes in volume or electrolyte excretion were expected to occur. Normal subjects and patients with advanced renal insufficiency were given constant intakes of water but varying quantities of sodium or potassium while fasting. Also, consecutive voidings and consecutive twenty-four-hour collections were followed in patients with advanced renal insufficiency and in patients with acute renal failure.

In normal subjects changes in sodium and potassium excretion were gradual, although at times considerable and quite independent of wide changes in urine volume, with corresponding variations in urine concentrations. In the patients with advanced renal insufficiency under similar test conditions, urine volumes and concentrations and hence electrolyte excretions showed in general less variation as compared with the normal responses. The diurnal and day-to-day changes in the patients studied showed close correlation between urine volume and electrolyte excretion associated with almost constant urine concentrations, particularly of potassium. This urine electrolyte concentration was much higher in the patients with severe renal failure, acute or chronic, than has been

observed in patients with normal renal function and minimal urine levels.

Several of the patients with high constant urine potassium concentrations had low serum potassium values. Administration of additional potassium resulted in a considerable uptake before the urine concentration rose. In most of these patients this constant urine potassium level lay between 20 and 35 mEq./L. in spite of two- or three-fold changes in urine volume. This suggests that patients with severe renal insufficiency probably are subject to loss of potassium as well as sodium in the urine.

QUANTITATIVE ESTIMATE OF VASOMOTOR TONE IN THE HUMAN EXTREMITY WITH COMPARATIVE STUDIES OF THE SYMPATHETIC BLOCKING AND ADRENOLYTIC PROPERTIES OF TETRAETHYLAMMONIUM, PRISCOL AND DIHYDROERGOCORNINE. *John W. Avera, M.D., Sibley W. Hoobler, M.D., Samuel G. McClellan, M.D. and William J. Little, M.D. Ann Arbor Mich.*

Presumably complete blockade of sympathetic vasomotor tone in the human subject without marked organic vascular disease was produced by means of spinal anesthesia, caudal anesthesia, lumbar paravertebral block or within twenty-four hours after sympathectomy. Blood flow to the foot as measured by the venous occlusion plethysmograph was regularly increased to an average of fourteen times control values. In contrast, tetraethylammonium (500 mg. intravenously) increased the blood flow on an average seven times the resting levels and produced no vasodilatation after sympathectomy or after intra-arterial administration. In usual clinical doses it therefore produced an approximately 50 per cent blockade of sympathetic vasoconstrictor tone and had no local vasodilator action.

Priscol (30 to 50 mg. intravenously) induced a three-fold increase in the blood flow in the foot and a two-fold increase in the innervated and denervated hand. The blood flow likewise was increased after intra-arterial injection. In this dosage the effects of the drug can in large measure be accounted for by a local vasodilator action although slight sympatholytic activity cannot be excluded.

Dihydroergocornine (0.25 to 1 mg. intravenously) caused a slow and delayed increase in the blood flow to 2.6 times the resting levels

in the foot and 2.1 and 2.4 times the resting levels in the innervated and denervated hand, respectively. In this dosage the drug has little or no sympatholytic effects and may produce vasodilatation after conversion into a vasodilator agent or by altering existing vasoregulatory mechanisms which are not mediated through sympathetic pathways.

Adrenolytic activity was measured by determining the effect of the drugs on the vasocon-

strictor response to an intra-arterial injection of epinephrine. When tetraethylammonium, DHO or benzodioxane (16 mg.) were administered intravenously, the response to intra-arterial epinephrine was not altered. On the other hand, administration of priscot intravenously had a moderate adrenolytic effect. When high local concentrations of the last three drugs were achieved by intra-arterial injection, significant adrenalin blocking action was demonstrated.

Case Reports

Diffuse Progressive Interstitial Fibrosis of the Lungs*

A. J. BEAMS, M.D. and O. HARMOS, M.D.

Cleveland, Ohio

WE wish to report an unusual case of fatal pulmonary disease which presented at autopsy many of the features of acute diffuse interstitial fibrosis of the lungs, a disease first described by Hamman and Rich.¹ The clinical course of the present case differed from those which they described in that its duration was fifteen months instead of four to twenty-four weeks.

CASE REPORT

A. G., a single white thirty-two year old merchant seaman, was admitted to the U. S. Marine Hospital complaining of cough and shortness of breath. He was first admitted for this complaint on January 2, 1946. For three months before admission the patient had experienced some shortness of breath on exertion and for one month he had a cough which was productive occasionally of blood-streaked sputum and pain in the anterior chest.

Physical examination revealed nothing which was of any help in explaining the patient's symptoms. A roentgenogram of the chest (Fig. 1) showed hazy shadows in the lower half of the left lung and the lower fourth of the right immediately above the diaphragm. The heart and aorta were within the normal limits of size and contour. The roentgenologist considered these changes characteristic of atypical pneumonia. However, when a second roentgenogram made three weeks later showed no changes, a chronic, infection-producing pulmonary fibrosis was considered as another possibility. The laboratory studies which included repeated sputum examinations and blood studies added nothing to the solution of the problem. The patient was afebrile during his entire course of thirty-six

days in the hospital. His shortness of breath improved and the cough disappeared.

His second admission to the hospital was on June 6, 1946, when he complained of symptoms similar to those experienced at the time of his first admission. After discharge from the hospital on February 7, 1946, he was free of symptoms until May when he had a return of his cough and shortness of breath which gradually grew worse until his second admission to the hospital.

The physical examination did not yield any more information at this time than it did at the first admission. His temperature was 37°C., pulse 90, respiration 22 and blood pressure 124/78. He was well nourished and did not appear acutely ill. There was a slight diminution in the intensity of the breath sounds at the base of the right lung. The heart was normal in size and no murmurs were heard. A roentgenogram of the chest showed only a slight change from that made five months previously. Streaky, fine, mottled shadows were present in both lung bases involving the lower half of the left lung and the extreme base of the right lung where there appeared to be an increase in the shadows. Since streaky and hazy shadows in both lung bases with little change on serial films had persisted for a period of five months, it was concluded that some chronic infection-producing fibrosis such as pneumoconiosis or sarcoidosis was responsible for these changes. The other laboratory studies added no information. The red blood cell count was 5,050,000, hemoglobin 12.2 Gm., white blood cell count 9,000 with 64 per cent neutrophils, 31 per cent lymphocytes and 5 per cent eosinophils. The sedimentation rate was 18 mm. per hour. The serologic test for syphilis was negative. The urine showed no abnormal findings; sputum examinations for

* From the Departments of Medicine and Pathology, U. S. Marine Hospital, Cleveland, O. Approved for publication by the Surgeon General, U. S. Public Health Service.



FIG 1



FIG 2

FIG 1 Roentgenogram of the chest taken January 3, 1946, showing hazy shadows in the lower half of the left lung and the extreme base of the right

FIG. 2 Roentgenogram taken August 14, 1946, showing an increase in the mottled and hazy shadows in both lungs. Changes noted in the contour of the heart and the prominence of the pulmonary vessels suggested *cor pulmonale*

tubercle bacilli and for fungus infection were negative.

For the first nine weeks in the hospital the patient was ambulatory. During this time no change was noted except a slight increase in dyspnea. An x-ray of the chest made July 12, 1946, showed very little change from the one made a month previously. At the end of the tenth week in the hospital (August 8th) his dyspnea became much worse and a few rales were heard at the bases of both lungs. A systolic impulse and a diastolic impact were palpable over the right ventricle suggesting enlargement. A roentgenogram of the chest (Fig. 2) made August 14th showed progressive changes in the lungs with streaky, mottled and hazy shadows in the middle third of both lungs and upper third of the left lung just below the clavicle. *Cor pulmonale* was suggested by the increased prominence of the pulmonary vessels and filling of the incisura of the left upper border of the heart. On August 18th the patient's condition suddenly showed a marked change; his respiratory rate rose to 50 and he became extremely cyanotic. The only other changes which were noted at this time were a great

increase in palpable precordial activity and more numerous rales at the bases of the lungs. Administration of oxygen by means of a tent produced a decrease in both the cyanosis and dyspnea. From this time until his death, December 12, 1946, he was never able to be out of the tent for more than thirty-minute periods. The cyanosis and dyspnea gradually increased in spite of oxygen therapy. There were no significant changes noted in the lungs but there was an increase in the palpable activity over the right ventricle; the pulmonic second sound was accentuated and the veins of the neck were distended. No other signs of cardiac failure were observed during the course of illness except for the last x-ray of the chest made November 18th at the bedside which showed dense, patchy, hazy shadows throughout both lungs suggesting pulmonary edema. The pulmonary vessels were very prominent and there was an increased bulging of the left upper border of the cardiac shadow. Another interesting development was clubbing of the fingers which was observed about four weeks after the cyanosis appeared. The only significant change in the laboratory studies was an increase in red cell count and

hemoglobin. The red cell count rose to 7,110,000 and the hemoglobin to 18.9 Gm. The white cell counts were normal throughout the illness until one month before death when they rose to 16,000. The patient remained afebrile until August 28th and then the temperature ranged from 37°C. to 38°C. until six days before death when it gradually rose, reaching a peak of 39.2°C. He died on the 189th hospital day. It was thought that the immediate cause of death was pneumonia.

The autopsy was limited to the chest. Some mucopurulent exudate coated the tracheal lining. No collection of fluid or pleural adhesions was found about the lungs. The left lung weighed 750 Gm. and the right 850 Gm. The upper lobes of the lungs presented the appearance of an almost uniform pneumonic consolidation. A deep, reddish color prevailed on the cut surface of the left upper lobe and a mottling of greyish and brownish areas appeared on the right side. The lower lobes indicated an uneven firmness to palpation; firm, greyish and somewhat granular areas were distributed throughout these lobes on section. Frequent areas of emphysema were enclosed by the interlacing, dense, fibrotic portions of the lower lobes and groups of emphysematous blebs occurred at peripheral locations. (Fig. 3.) An exudate was expressible from frequent bronchi. No thrombi were observed in the blood vessels.

The histopathologic findings were much the same as those described in the cases of Hamman and Rich, an opinion confirmed by Dr. A. R. Rich. Microscopically, a widespread interstitial fibrosis was noted in all lobes. The left upper lobe showed considerable obliteration of the normal alveolar spaces due to pronounced thickening and some hydropic changes of the alveolar walls. Many dilated capillary blood vessels occupied most parts of the walls of the alveoli and some proliferation of fibroblasts was noted about these vessels. Strips of fibrinohyaline membranes were conspicuous in or about frequent alveoli and some of the air vesicles contained clumps of fibrin, leukocytes and desquamated epithelial cells or collections of red corpuscles. (Fig. 4.) In the lower half of the lobe there was a gradual change from the congestion and prevalence of capillary vessels to a very unusual and pronounced proliferation of connective tissue in and about the alveolar walls which was true in all of the other lobes. There were widely distributed beady or patchy



FIG. 3. An almost uniform consolidation is exhibited on the cut surface of the upper lobe. The firmness of the lower lobe is interrupted by frequent foci of emphysema. Several borders of the lobes show emphysematous blebs.

fibrotic areas and partial obliteration of the alveolar spaces. The epithelium of the alveoli frequently was composed of prominent, high epithelial cells, some of which were unusually large, causing the epithelium to be irregular in places. (Fig. 5.) Occasionally parts of the alveolar epithelium were absent and in some regions the nuclei of the epithelial cells were indistinct or fragmented.

A number of bronchi contained some fibrinocellular exudate. In very occasional parts of the bronchi or bronchioles the epithelium was vacuolated or indistinct and the lumina of some of the small bronchi were narrowed or obliterated. The linings of several bronchi showed squamous-celled metaplasia and, rarely, minute peripheral spots of heteroplastic ossification occurred in lung sections. The interstitial areas were frequently seats of small groups of lymphocytes, pigment-bearing phagocytes, loose collections of histiocytes and plasma cells, scattered giant cells and eosinophiles. In addition, frequent groups of dilated capillary vessels were noted and islets of large, epithelial-type cells were



FIG. 4

FIG. 4. A field from the upper lobe of the left lung which shows greatly thickened alveolar walls occupied by dilated capillary vessels. Note the loose collections of wandering cells, incipient proliferation of fibroblasts and hyaline membranes lining alveolar spaces; $\times 210$.



FIG. 5

FIG. 5. Advanced proliferation of connective tissue is seen in and about the alveolar walls with much narrowing of the alveoli in the upper half of the field. Note the beady character of the fibrosis in the upper half of the field, the frequently prominent alveolar lining epithelium and heaping of epithelial cells: $\times 210$.

conspicuous in several sections; however, we believe that these heaps of cells were within deformed or collapsed air vesicles or represented proliferations of the alveolar epithelium. Focal emphysema involving a considerable number of alveoli was a conspicuous finding, especially in the lower pulmonary lobes. The branches of the pulmonary arteries indicated no intimal thickening of significance. The tracheobronchial lymph nodes were congested and enlarged; microscopically, occasional collections of mononuclear and plasma cells were present in the sinuses.

The heart was moderately enlarged and somewhat flabby in consistency; it weighed 470 Gm. The right ventricle was dilated and its musculature indicated hypertrophy, showing an average thickness of 6 mm. The left ventricle measured 12 mm. in thickness. The valves and the coronary vessels showed no remarkable lesion and the microscopic appearance of the myocardium was essentially normal. A mild intimal sclerosis of the aorta was noted.

COMMENTS

The pathologic studies indicate that the proliferative fibrotic process was most ad-

vanced in the lower lobes while parts of the upper lobes presented a more recent lesion. The histologic sections of the case reproduced most of the pathologic peculiarities described by Hamman and Rich, as follows: (1) There was a diffuse and progressive interstitial proliferation of connective tissue throughout all lobes of both lungs; this tissue production showed varying stage of development and activity. A rather moderate degree of inflammation, recent and old, was noted; however, it differed from lesions present in ordinary pneumonia of bacterial origin. For analogy we quote Rich: "The essential peculiarity in this condition is the remarkable proliferation of connective tissue that occurs within the alveolar walls, even in the absence of the organizing exudate in the related alveolar spaces. One can find virtually all stages of the process, from the acute inflammatory phase, to complete fibrosis. It is quite clear that the attack on the lungs in this condition does not begin everywhere at once, but rather, spreads from place to place until all lobes of both lungs have become diffusely

involved with lesions in different stages of development." (2) a proliferation of capillary blood vessels and hydropic changes were noted at places in the alveolar walls; hyaline membranes lined the alveoli and a moderate degree of inflammation was observed. (3) Proliferation and prominence of the lining alveolar epithelial cells, frequently resembling the bronchiolar epithelium, were present. (4) There was stenosis of some small bronchi and bronchioles with emphysematous dilatation of the adjacent alveoli. (5) No stainable bacteria were demonstrated in the pulmonary parenchyma and a smear of the bronchial exudate showed pairs of gram-negative and gram-positive cocci. The only differences noted in the histologic examination from those described in the cases of Hamman and Rich were that there were less edematous changes; no striking numbers of eosinophilic cells were found; the necrosing changes in the alveolar and bronchial epithelium were infrequent; and the thickening of the alveolar walls frequently exhibited a remarkable beady appearance.

In this case the clinical course can be divided into two stages; first, a latent period of eleven months and second, an active phase of four months. During the first ten and one-half months of the latent period very little progression of the disease was noted. There were no physical findings during this time to explain the shortness of breath and cough; however, the roentgenogram showed changes at the bases of both lungs which suggested pulmonary fibrosis. In the last two weeks of this period the dyspnea became worse; a few rales were heard at the bases of both lungs and cor pulmonale was suggested by the increased palpable activity of the right ventricle and the roentgenologic changes noted in the cardiac shadow.

The active phase of the disease began abruptly and followed a course similar to those described by Hamman and Rich and Eder, Hawn and Thorn.² This sudden change, manifested by cyanosis and marked dyspnea which was never completely re-

lieved by oxygen therapy and gradually became worse over a period of four months, could not be explained adequately by any changes found in the lungs. The sudden onset suggested heart failure; however, the only signs indicating this were an increase in precordial activity, distention of the veins of the neck and the changes in the roentgenogram made one month before death which suggested pulmonary edema.

The histologic changes found in the lungs offer an explanation for the failure of oxygen to give the expected relief of the dyspnea and cyanosis and the disparity between the subjective symptoms and the physical findings in the lungs. A great increase in the connective tissue was noted in the alveolar walls which must have completely obstructed the exchange of gases in the alveoli where the process was well-advanced. As the respiratory membrane of the lung was reduced the dyspnea and cyanosis increased and the response to oxygen administration became less. In addition to interfering with the exchange of gases a reduction of the pulmonary vascular bed occurred producing an increase in pressure in the pulmonary artery resulting in cor pulmonale. The great disparity between the subjective symptoms and physical findings is easy to understand since the pathologic changes were confined chiefly to the alveolar walls.

SUMMARY

1. An unusual case of fatal pulmonary disease has been presented. The clinical and pathologic aspects have been discussed.

2. This case differed from those described previously in that the duration of the disease was fifteen months instead of four to twenty-four weeks.

3. Observation of the course of the disease throughout the latent period of eleven months and the active period of four months offered us an opportunity to observe the development of cor pulmonale, clubbing of the fingers and polycythemia.

4. In view of the longer duration of the disease in this case we propose to employ

the term “diffuse, progressive, interstitial fibrosis of the lungs.”

We wish to thank Doctor Carol Dundon for his cooperation and interest in the interpretation of the x-ray films and Doctor Herbert Z. Lund for his helpful suggestions in the pathologic studies.

REFERENCES

1. HAMMAN, LOUIS and RICH, ARNOLD R. Acute diffuse interstitial fibrosis of the lungs. *Bull. Johns Hopkins Hosp.*, 74: 177-212, 1944.
2. EDER, HOWARD, HAWN, CLINTON V. and THORN, GEO. Report of a case of acute interstitial fibrosis of the lungs. *Bull. Johns Hopkins Hosp.*, 76: 163-171, 1945

A Syndrome Characterized by Generalized Cutaneous Eruption, Chorioretinitis and Eosinophilia, Probably Due to Chronic Toxoplasma Infection*

ANDREW J. BRENNAN, M.D., THOMAS MCP. BROWN, M.D., JOEL WARREN, PH.D.
and GEORGE VRANIAN, M.D.

Washington, D. C.

INFECTION with toxoplasma parasites can produce a variety of clinical syndromes in man. This obligate intracellular protozoan has been shown to be the cause of a congenital encephalomyelitis of the newborn,¹ an acute encephalitis in children,² a typhus-like syndrome of adults associated with pneumonitis,³ an acute febrile illness in adults clinically similar to trichinosis⁴ and non-apparent infections in adults detected by finding circulating antibodies against this parasite.⁵

It is the purpose of this paper to describe a heretofore unreported type of chronic illness characterized by the presence of a generalized cutaneous eruption, chorioretinitis and eosinophilia. Antibodies against toxoplasma were present in the blood of the patient and a positive skin test was obtained when toxoplasma antigen was injected intradermally into this individual. However, several attempts to isolate toxoplasma from the patient's blood, sternal marrow and spinal fluid were unsuccessful.

CASE REPORT

A white male, aged thirty, was admitted to the Veterans Administration Hospital, Washington, D. C., on September 24, 1947. He had been a well-driller prior to military service. There was no history of prolonged contact with animals or arthropods. In 1943 the patient

developed a bilateral iritis together with symptoms of anorexia and severe epigastric pain which were unrelated to intake of food and not relieved by medication. Roentgenograms showed the duodenum to be irregular and there was evidence of crater formation on its superior and anterior wall. He was discharged from the service in 1943 with a diagnosis of duodenal ulcer. These symptoms persisted until the present hospital admission. In December, 1945, tender nodules varying in diameter from a few mm. to 5 to 6 cm. began to appear under the skin. They usually occurred in crops and persisted for four to six weeks and then gradually subsided. The nodules at various times have appeared over the entire body including the soles of the feet and the scalp. Crops of small vesicles varying from 2 to 4 mm. in diameter and containing clear fluid were also noted. The vesicles promptly became hemorrhagic and were the sites of intense pruritus. Dark brown scabs formed following rupture of the vesicles and after several weeks these scabs separated from the skin surface, leaving reddened areas which eventually faded but left atrophic scars similar to the residual lesions of smallpox. Nodules and vesicles of this type recurred continuously from 1945 to 1948. Pain was often present in the lower extremities from the onset of this illness. In addition the patient complained of weakness, severe headache, loss of weight and intermittent fever. There was a history of two attacks of Bell's palsy, the first involving the right side in July, 1944, and the second occurring on the left in March,

* From the Veterans Administration Hospital, Washington, D. C., and the Department of Virus and Rickettsial Diseases, Army Medical Department Research and Graduate School, Army Medical Center, Washington, D. C. This paper is published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by us.



FIG 1 Appearance of patient on November 25, 1947

1947. There was complete recovery from each attack. A biopsy of a subcutaneous nodule was taken three months before entering Veterans Administration Hospital. On the basis of its histopathology a diagnosis of dermatomyositis was made.

Physical examination revealed the patient to be a well developed, fairly well nourished white male who nevertheless appeared chronically ill and older than his stated age. His hair was prematurely gray. Examination revealed an old area of chorioretinitis approximately the size of the optic disc in the periphery of the left fundus, a small ulcerative lesion about 5 mm. in diameter on the right tonsil and multiple, raised, tender, erythematous, subcutaneous nodules scattered diffusely over the trunk and extremities. In addition, innumerable cutaneous lesions were present. These were in various stages of development from vesicles with crusted surfaces to erythematous and non-erythematous scars of varying size. (Fig. 1.) No other abnormalities were noted in the physical examination.

Clinical laboratory data was as follows. Blood count on admission: red blood cells, 4,600,000; hemoglobin, 14 Gm.; white blood cells, 11,150:

polymorphonuclears, 74; lymphocytes, 19; monocytes, 3 and eosinophiles, 4. The sedimentation rate was 30 mm. in one hour corrected (Wintrobe). Throughout the hospital stay the red blood cells ranged between 4,040,000 and 4,630,000, white blood cells between 5,900 and 11,150. There was little change in the differential counts except for an eosinophilia which reached 14 per cent. Urinalysis on admission: specific gravity, 1.022; albumin, very faint trace; sugar, negative; microscopic examination, 10 to 20 white blood cells, 8 to 10 red blood cells and a few hyaline and fine granular casts. Subsequent urinalyses were within normal limits except during a period of therapy when numerous red blood cells and sulfadiazine crystals were seen. The cytology of the sternal bone marrow was normal. All bacteriologic studies were negative. A complement fixation test for histoplasmosis was positive to a titer of 1:32 in one instance but on repeated examination one month later was negative. Intravenous phenolsulfonphthalein, uric acid clearance and Fishberg concentration tests were within normal limits. X-ray examinations of the skull, chest and gastrointestinal tract were negative. Oscillometric readings of the lower extremities were within the normal range. There were no electrocardiographic abnormalities.

A biopsy of a skin lesion and subcutaneous nodule was taken on September 25, 1947. The histologic findings were not pathognomonic for any pathologic entity. The tissues revealed infiltrations with numerous eosinophiles; severe vascular changes were also present and suggested a so-called "hyperergic" type of inflammation. (Fig. 2.) *Toxoplasma* were not observed in a careful examination of numerous sections of this material.

Three attempts were made to isolate *Toxoplasma* from the patient's blood. On October 21, 1947, heparinized blood was injected intracerebrally and intraperitoneally into each of ten mice and two guinea pigs. On November 5, 1947, a second specimen of blood was obtained and inoculated into the chorio-allantoic sac of ten embryonated eggs, and into two guinea pigs by the intradermal and intraperitoneal routes. Spinal fluid also taken at this time was injected into ten embryonated eggs. The third attempt at isolation was performed on November 24, 1947, when 25 cc. of heparinized blood was centrifuged at 3,500 revolutions per minute for twenty minutes and the sediment resuspended

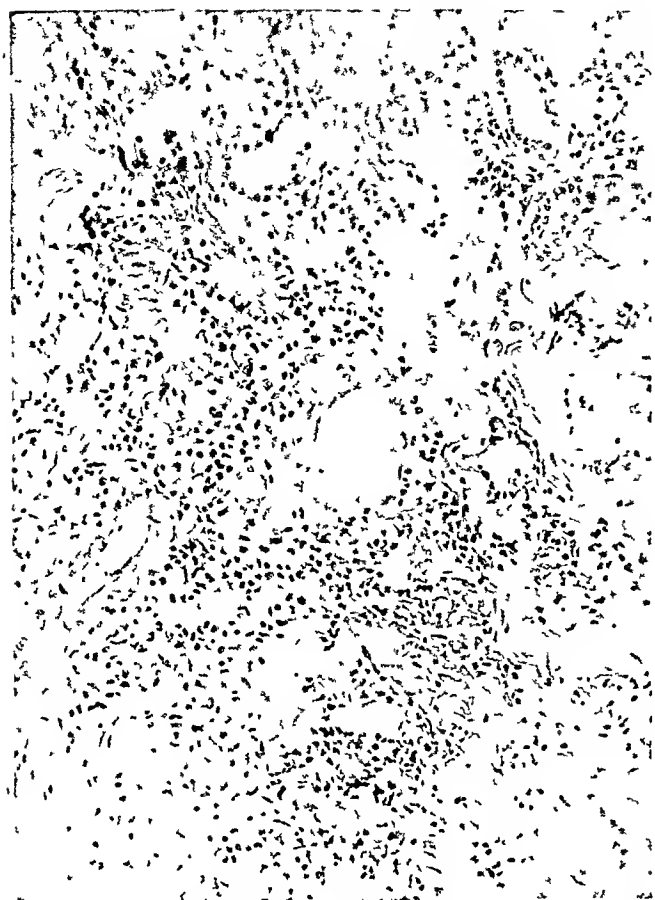


FIG. 2. Section through a biopsied portion of a cutaneous lesion, $\times 300$.

in 5 cc. of physiologic saline solution. This material was then inoculated intraperitoneally into mice, guinea pigs and into the chorio-allantoic sac of embryonated eggs. At this time also sternal marrow was aspirated from the patient and injected into mice and guinea pigs.

None of these inoculations produced any signs of disease in the animals or embryonated eggs. Furthermore, serial blood passages which were performed in a number of instances also gave negative results. The failure of the guinea pigs to develop specific complement-fixing antibody of toxoplasmosis indicated the absence of even subclinical infection.

Complement fixation tests were performed to determine the toxoplasma antibody level in the patient's serum taken on October 19, 1947 and November 5, 1947. Both serum specimens fixed complement at a dilution of 1:128 when tested with toxoplasma antigen prepared from infected chorio-allantoic membrane.⁶ Furthermore, both sera gave strongly positive reactions in neutralization tests carried out in rabbits inoculated intradermally.

On the basis of these positive serologic reactions it was decided to perform an intradermal skin test on this patient, employing an antigen



FIG. 3. Appearance of toxoplasma skin test forty-eight hours after inoculation. Toxoplasma antigens injected into left forearm, control on right arm, *a*, control; *b*, spontaneous lesion, *c*, induced lesion.

derived from toxoplasma-infected chorio-allantoic membrane.⁶ The antigen was prepared as follows: A 10 per cent suspension of infected membranes in physiologic saline solution was rapidly frozen and thawed three times to destroy the toxoplasma and then centrifuged at 3,000 revolutions per minute for fifteen minutes. The supernatant fluid was removed and sufficient merthiolate added to make a final concentration of 1:10,000. After this material had been shown to be bacteriologically sterile and non-infectious for mice and guinea pigs it was used as a skin test antigen. A suspension of normal chorio-allantoic membrane prepared in a similar fashion served as a control antigen. On November 24, 1947, the patient was inoculated intradermally with 0.1 cc. amounts of 1:1,000 and 1:100 dilutions of the control and toxoplasma antigens. There was no immediate reaction at either site. Sixteen hours later a slight reaction was noted at the site of the injection of the 1:1,000 dilution of toxoplasma antigen and a raised erythematous area measuring 1.0 by 1.0 by 0.2 cm. at the site of the injection of the 1:100 dilution of toxoplasma antigen. Forty-eight hours following the skin test the site of the 1:100 dilution measured 1.5 by 1.5 by 0.3 cm. (Fig. 3.) At this time the lesion became pruritic and a small vesicle appeared which was indistinguishable from the cutaneous lesion previously described on the patient. Seventy-two hours after injection the lesion had become slightly discolored and hemorrhagic in appearance, resembling a spontaneous cutaneous lesion. No visible reactions were present at the control sites. Examination of a biopsy specimen of the skin obtained from the site of injection of



FIG. 4. Section through a biopsied portion of an induced skin lesion resulting from the intradermal inoculation of an extract of toxoplasma-infected chorio-allantoic membrane; $\times 300$

the 1:100 dilution of toxoplasma antigen on the ninth day after inoculation revealed a histologic picture (Fig. 4) similar to that of the spontaneous skin lesion.

From the date of admission until November 25, 1947, the patient's symptoms persisted unabated. His temperature ranged from 98.6°F. to 102.0°F. and during this period he was afebrile on only three occasions which lasted five days, two days and three days, respectively. He was seen by a dermatologist who indicated that the skin eruption was compatible with the diagnosis of erythema multiforme bullosum. Because of the data suggesting a diagnosis of toxoplasmosis, and in light of the experimental work done by Sabin and Warren on the use of certain sulfonamides in the treatment of laboratory animals infected with toxoplasma,⁷ sulfadiazine therapy was instituted on November 25, 1947, using 6.0 Gm. daily. For ten days prior to the initiation of therapy the patient's temperature ranged from 98.6°F. to 101.8°F. Within twenty-four hours after administration of sulfadiazine the patient's temperature dropped to normal and he remained afebrile for a period of twelve days.



FIG. 5. Appearance of patient December 22, 1947, twenty-seven days after beginning of sulfonamide therapy

The muscular and epigastric pain markedly decreased in severity and duration, his appetite improved, the headaches disappeared and there was a marked decrease in the formation of new nodules and vesicles (Fig. 5.) Prior to therapy he required analgesic drugs for the relief of pain but none were necessary during this afebrile period.

On December 5, 1947, the patient had a sulfadiazine level of 20.2 mg. per cent. Because of this high level therapy was discontinued for twenty-four hours. At the end of this interval the level had dropped to 13.8 mg. per cent and sulfadiazine was again instituted but with the dose reduced to 4.0 Gm. per day. In spite of continued medication the patient's temperature again became elevated, ranging between 99°F. to 100.6°F. for two days, following which he was essentially afebrile for thirteen days. At this time (December 27, 1947), he developed hematuria which necessitated discontinuance of sulfadiazine. Following this his symptoms, with the exception of epigastric pain, reappeared but his temperature ranged between normal and 99.5°F. The rate of formation of new nodules and vesicles

returned to the pretreatment level. On January 17, 1948, the therapy was modified and sulfapyridine alone, 1 Gm. daily, was started and increased to 2 gm. daily on January 28, 1948. It then became imperative for him to leave the hospital for personal reasons and he was discharged on February 2, 1948. Correspondence received from the patient on June 3, 1948, indicated that his condition was similar to that on admission.

COMMENTS

The rather bizarre clinical features observed in this patient suggested several possible diagnoses: among these were periarteritis nodosum, erythema multiforme and toxoplasmosis. All but the latter were discarded when the positive serology for toxoplasma was discovered.

It seemed to us not unlikely that this man's present illness probably dated back as far as 1943 at which time a diagnosis of duodenal ulcer and bilateral iritis was made. The occurrence of two episodes of Bell's palsy, first in 1944 and again in 1947, suggested that injuries to the central nervous system might have occurred at or shortly after the appearance of iritis and the cutaneous lesions previously noted.

The finding of strongly positive complement fixation, neutralization and skin sensitivity tests for toxoplasma made it possible to account for many of the puzzling features of this case. The chorioretinitis, headache and fever are in accord with the pathologic changes known to be caused by this parasite. Toxoplasma are transported in the blood stream and invade and multiply in any of the mesenchymal tissues of the body. Their final localization is apparently determined by: (1) chance, (2) mechanical effects, as the filtering action of the lung and spleen and (3) factors as yet unknown. It is not unlikely that this non-selective localization accounts for the varied manifestations often observed in human toxoplasmosis. The long duration of illness in our patient also has a parallel in the well established fact that chronic toxoplasmosis exists in animals¹ and it is most probable that a chronic infection exists for a con-

siderable time in the mothers of infants who are born with congenital toxoplasmosis.⁵

The case described in the present report is distinguished by an eosinophilia and the appearance of crops of nodular or vesicular lesions involving the epidermis and subcutaneous layers of the skin. Although no parasites were observed in the tissue at these sites, the histopathology of these nodules is essentially identical with the response elicited by the intradermal inoculation of a toxoplasma antigen. The histologic picture is also similar to that induced by the injection of any reagin into a hyperergic individual.¹⁰ It is our opinion that the continued appearance of these cutaneous lesions is due to the constant release of living toxoplasma or toxoplasma antigen from one or more internal foci. These parasites, finding their way into the smaller capillaries, evoke an allergic reaction in this individual but in the presence of the high level of humoral antibody are unable to multiply to any extent and the cutaneous lesion eventually recedes. The repeated failure to isolate toxoplasma from this patient will be raised as an argument against this hypothesis. However, it should be noted that the number of circulating parasites even in heavily infected experimental animals is often small.⁹ Furthermore, it will be recalled that several cases of human toxoplasmosis have been reported in which toxoplasma could not be isolated from the blood or spinal fluid.^{11a,b}

Following administration of sulfadiazine this patient exhibited marked improvement in his general condition. After twenty-two days of this therapy he unfortunately developed hematuria which made it necessary to discontinue the drug. His subsequent course has not been improved. Unfortunately no alternative therapeutic agents to the sulfonamides are presently available for the therapy of human infection from toxoplasma.

SUMMARY

The case of a thirty year old male exhibiting generalized cutaneous eruption,

chorioretinitis and eosinophilia of three years' duration is described. Serologic tests and an intradermal skin test for toxoplasmosis were strongly positive. Sulfonamide therapy was beneficial but the appearance of hematuria necessitated discontinuance of the drug. Following this the patient's condition deteriorated. The possible etiology of this case is discussed.

REFERENCES

1. WOLF, A., COWEN, D. and PAIGE, B. H. Toxoplasmic encephalomyelitis. *Am. J. Path.*, 15: 657, 1939.
2. SABIN, A. B. Toxoplasmic encephalitis in children. *J. A. M. A.*, 116: 801, 1941.
3. PINKERTON, H. and WEINMAN, D. Toxoplasma infection in man. *Arch. Path.*, 30: 374, 1940.
4. SYVERTON, J. T. and SLAVIN, H. B. Human toxoplasmosis. *J. A. M. A.*, 131: 957, 1946.
5. SABIN, A. B. Toxoplasma neutralizing antibodies in human beings and morbid conditions associated with it. *Proc. Soc. Exper. Biol. & Med.*, 51: 6, 1942.
6. WARREN, J. and RUSS, S. Cultivation of toxoplasma in embryonated eggs. An antigen derived from chorioallantoic membrane. *Proc. Soc. Exper. Biol. & Med.*, 67: 85, 1948.
7. SABIN, A. B. and WARREN, J. Therapeutic effectiveness of certain sulfonamides on infection by an intracellular protozoan (Toxoplasma). *Proc. Soc. Exper. Biol. & Med.*, 51: 19, 1942.
8. SABIN, A. B. and OLITSKY, P. K. Toxoplasma and obligate intracellular parasitism. *Science*, 85: 336, 1937.
9. WEINMAN, D. Chronic toxoplasmosis. *J. Infect. Dis.*, 73: 85, 1943.
10. FORBUS, W. D. Reaction to Injury. Pp. 134-135. Baltimore, 1943. Williams & Wilkins Co.
- 11a. SABIN, A. B. Toxoplasmosis. Brennemann's Practice of Pediatrics. Vol. 4, W. F. Prior Co. Hagerstown, Md., 1943.
- b. MILLER, M. C. Infantile toxoplasmosis. *J. Pediat.*, 30: 201, 1947.

Editorial

Treatment of Auricular Flutter with Digitalis

THE use of digitalis in auricular fibrillation has been clearly defined on a rational basis for many years. Every doctor is familiar with the principle of slowing the ventricle by means of this drug, and all agree on the need of maintaining a slow ventricular rate by adequate continuous dosage. Restoration of normal mechanism is not usually anticipated and should it occur is regarded as a coincidence or perhaps the result of improved cardiac function. It is confusing, therefore, to find in most discussions of the treatment of auricular flutter—a condition so closely related to fibrillation—an entirely different prescription for the use of digitalis. It is the fact that this prescription, obviously obsolete, is still given in some widely used recent textbooks which prompts the following remarks.

The procedure, as described, is essentially as follows: Digitalis is given in large doses until the ventricle is slowed just as in cases of fibrillation. The drug is continued up to the point of tolerance, whereupon within a few days flutter may be expected to pass over to fibrillation. But now instead of continuing digitalis the drug is stopped altogether, whereupon a normal mechanism is said often to supervene within a few hours or days. It should be emphasized that the crucial point in the prescription is the stopping of digitalis as soon as fibrillation comes on; it is implied that continued administration of the drug at this point may prevent the return of a normal mechanism. Inasmuch as this prescription is so directly

at variance with the established usage of digitalis in auricular fibrillation, one must examine the results which have been obtained with it as well as its theoretic validity.

It appears that the first to suggest for auricular flutter the procedure outlined above (in future referred to as the "classical therapy") was Sir Thomas Lewis in his paper of 1912.¹ In the case described in detail digitalis was given until 4:1 block and later auricular fibrillation supervened. Digitalis was stopped but after eight days fibrillation was still present. Two weeks later the patient was found to have a normal mechanism. It was in a subsequent paper,² however, that Lewis described more cases and became more emphatic in defining the "classical therapy." He concluded that "Even when it has been present many months, flutter may often be abolished by the administration of digitalis. This drug induces temporary fibrillation and (if digitalis is stopped) the normal rhythm is subsequently restored and may persist." In the following year Ritchie³ in his book on auricular flutter reported other cases in which the classical procedure was used. Ritchie remarked (p. 107) that "the fourth phase (of digitalis effect) is characterized by restoration of physiological rhythm. In some instances this may occur while the

¹ LEWIS, T. Observations upon disorders of the heart's action. *Heart*, 3: 279, 1911-1912.

² Idem. Observations upon a curious and not uncommon form of extreme acceleration of the auricle. *Heart*, 3: 171, 1912-1913.

³ RITCHIE, W. T. *Auricular Flutter*. Edinburgh and London, 1914. W. Green & Co.

patient is still taking digitalis but as a rule not until the drug has been discontinued." . . . The restoration of the normal rhythm has been observed as early as the third or as late as the 23rd day after the patient has ceased taking digitalis."

It is of interest that the eight cases upon which the classical therapy is based do not really seem to give it strong support. First, flutter does not go over to fibrillation with any regularity. In the eight cases three failed altogether to fibrillate and in a fourth digitalis was given for a year before fibrillation supervened. In two more cases normal rhythm was not restored when digitalis was withdrawn. In only three of the eight cases did the prescribed sequence of events really unfold itself, and in these the interval between cessation of digitalis and resumption of normal mechanism varied greatly.

Ritchie³ in his final discussion of treatment (pp. 130-136) seems not entirely satisfied with the classical procedure. He points out that it worked in about only one-half of the cases and that even then there was likely to be a return to flutter or to

fibrillation. He raises the question of whether just enough digitalis to control the ventricular rate may not be better therapy than the large doses which are supposed to induce fibrillation.

Our own experience gives no support to the theory or practice of the classical therapy. We have seen patients with auricular flutter revert to a normal mechanism without any digitalis and with or without a recognized intervening period of fibrillation. Some patients have gone back to normal mechanism while on digitalis.

Flutter should therefore be treated with digitalis on the same basis as fibrillation. Should flutter go over to fibrillation the drug should not be stopped but continued in order to keep the ventricle slow just as in any instance of auricular fibrillation. There is no formula whereby return of normal mechanism can be regularly induced by the use of digitalis, and quinidine should be used if prompt restoration is to be attempted.

ARTHUR L. BLOOMFIELD, M.D.

Some Effects of Digoxin upon the Heart and Circulation in Man*

Digoxin in Left Ventricular Failure

RÉJANE M. HARVEY, M.D., M. IRENÉ FERRER, M.D., RICHARD T. CATHCART, M.D.,
DICKINSON W. RICHARDS, JR., M.D. and ANDRE COURNAND, M.D.

New York, New York

THE advent of the catheterization technic has not only prompted investigation of the hemodynamics of cardiac failure but also has stimulated renewed interest in the study of cardiovascular drugs in man. The entire problem of cardiac insufficiency is at present being re-examined in many clinical laboratories. Beyond differentiating high output and low output types of cardiac failure, little has been done to define in detail the complexity of the physiopathologic factors which may be involved in a single case. This definition is not only important to the better understanding of cardiac abnormalities but is crucial in any pharmacologic investigation. Therefore, it has become increasingly evident that a detailed analysis of both the clinical and physiologic status of the patient at the time of the drug study is essential. When the hemodynamic pattern is well defined, this analysis contributes much to the understanding of the natural history of certain disease processes and the subsequent physiologic alterations produced thereby. In addition it may afford the opportunity of isolating groups of cases with similar physiopathology.

Drug effects are frequently clarified when studied in groups of patients with similar hemodynamic patterns. The majority of investigations on the effect of digitalis

preparations have been carried out in patients with advanced heart disease in whom the physiologic alterations are mutually dependent one upon another and are numerous and complex and variable from one patient to another. In such cases it is often difficult to assess the exact mode of action of the drug. If, however, a group of patients is found in which the altered hemodynamics spring from a simple rather than a complex physiologic abnormality and the number of variables is minimal, a more precise delineation of the action of a drug on the circulation can be attempted.

Patients with pure left-sided heart failure comprise such a group. This type of case is difficult to find and hence this report includes observations on only five patients treated with digoxin. In order to elucidate the hemodynamic responses observed when left ventricular failure is relieved by medication an additional case of a patient with left ventricular failure treated with quinine is presented. As a contrast the effect of digoxin in one case of chronic cor pulmonale in congestive heart failure, chosen from a group of patients currently being studied, is discussed. The latter case illustrates the reaction of the circulation to digoxin when an entirely different state exists, namely, pure right-sided failure.

* From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Cardio-pulmonary Laboratory of the First Medical and Chest Services (Columbia University Division), Bellevue Hospital, New York, N. Y. The work described in this paper was supported by a grant from the Life Insurance Medical Research Fund, with additional support provided by the Commonwealth Fund.

MATERIAL AND METHODS

The six patients with left-sided failure include three with hypertensive cardiovascular disease, one with hypertensive cardiovascular disease and arteriosclerotic heart disease and two with rheumatic heart disease. The criteria used for diagnosis were those of the American Heart Association. The functional and therapeutic classification represents the status of the patient at the time of the study. It is worthy of comment that five of these patients had symptoms of paroxysmal nocturnal dyspnea, orthopnea and exertional dyspnea in varying degrees of severity but none had pulmonary rales or rhonchi. Of the five patients with symptoms four had an apical diastolic gallop. The patient receiving quinidine had been digitalized and had neither symptoms, signs nor gallop rhythm, but the hemodynamic studies revealed pulmonary hypertension, presumably due to left-sided heart failure.

The method of investigation used in this study was similar to that discussed in a previous report¹ with the exception that no sedation was used. A control electrocardiogram, including six precordial *v* leads and the augmented unipolar limb leads, was taken before introduction of the catheter and the intra-arterial needle. In all of these cases a double lumen catheter was used. This type of catheter permits registration of both right ventricle and pulmonary artery pressure curves throughout the study, eliminating further manipulation of the catheter once it is properly located. No attempt was made to secure right auricular mean pressures since the right ventricular end diastolic pressure is a better indication of the filling pressure of the right heart. Pressure curves were recorded by Hamilton manometers and analysis of them has been amply described previously.¹ A control cardiac output^{2,3} and blood volume determinations⁴ were done before administration of digoxin. All mixed venous blood samples were drawn from the pulmonary artery. Digoxin, 1.0 to 1.5 mg. in 30 cc. of physiologic saline, was injected through the catheter into the pulmonary artery over a five-minute period. Blood pressures were recorded at the conclusion of the injection and every ten to fifteen minutes for one to one and one-half hours thereafter. Two subsequent cardiac output determinations were made. The study was concluded with a second complete electrocardiogram. Heart rate was

computed from the electrocardiogram which was taken continuously on lead II. Total peripheral resistance was calculated as previously described.¹

It is obvious that maintenance of the patient in a constantly steady state is essential to this type of study. Any untoward reaction noted during the procedure demands correction of the underlying cause or immediate cessation of the investigation. A note of caution should be struck here concerning cardiac arrhythmias during catheterization. As was just mentioned the electrocardiogram was observed constantly throughout the study. Manipulation of the catheter tip in the tricuspid area and within the right ventricle frequently causes ventricular premature contractions to appear. In one hundred cardiac patients catheterized over a period of eighteen months transient right bundle branch block appeared during the procedure in two cases and the block disappeared as soon as the catheter was removed from the cavity of the right ventricle. Manipulation of the tip of the catheter in the region of the interventricular septum, especially at the outflow tract, may produce short runs of ventricular tachycardia. It is therefore inadvisable to leave the free tip of the catheter in the right ventricle for any length of time or to manipulate it back and forth across the pulmonic valve; hence the advantage of the double lumen catheter. The arrhythmias are not only in themselves potentially dangerous to the patient but radically alter the dynamics of the circulation, causing both blood pressure and cardiac output to change. In this group of one hundred cardiac patients no serious complications ensued from the catheterization procedure as a result of the strict precautions taken.

In any evaluation of changes produced by medication it is important to ascertain the range of variation expected with the technique employed—in this instance, the catheterization procedure. Ideally, such data should be obtained in a group of patients undergoing the same procedure but to whom no drug was given. In addition data could be obtained during control periods preceding administration of the drug. Tables I and II contain data on cardiac output determinations obtained in the former manner while in Table III are tabulated the blood pressure variations observed in a peripheral artery and in the right heart during the control periods before medication was given.

Control figures, shown in Table I, have been obtained by analyzing statistically the data on two separate and successive measurements of cardiac output in all the patients who had been studied solely for diagnostic reasons over the same eighteen-month period during which the

made in all but one patient in this series. The analysis of differences presented in Table II gives the mean difference and the range of variation to be expected when a second determination is made within approximately thirty minutes of the first. It can be concluded there-

TABLE I
STATISTICS OF TWO SUCCESSIVE DETERMINATIONS OF CARDIAC OUTPUT IN TWENTY CONTROL PATIENTS NOT RECEIVING MEDICATION

	First Determination			Second Determination		
	Mean	S.E.	Range	Mean	S.E.	Range
Oxygen consumption, cc./min./M. ²	140	±2.6	158-107	137	±2.3	156-119
Cardiac index, L./min./M. ²	3.46	± .19	5.01-2.03	3.42	± .19	5.19-2.02
A-V difference, volume per cent.	4.3	± .23	6.8-3.0	4.3	± .26	7.0-2.8
Pulse rate, beat/min.	77	± .35	117-54	76	± .35	117-52

Average time between two successive determinations = 27 minutes (range 11 to 60).

Average time between beginning of study and second determination = 148 minutes (range 48 to 186).

digoxin studies were pursued. None of these patients had congenital heart defects. They were studied by three different catheterization teams using the same laboratory and essentially the same procedure. None of these patients received any drug during the study nor were they subjected to any other procedures, such as pressure breathing or exercise. The average time between the first and second determinations was twenty-seven minutes and the length of time the patient was on the fluoroscopic table before the second determination was made averaged two and one-half hours.

It can be seen from Table I that the mean values of oxygen consumption, cardiac index, oxygenarteriovenous difference and pulse rate are almost identical in the first and second determinations. The correlation coefficient between the two successive determinations of oxygen consumption and two successive measurements of cardiac index are very high, respectively, $r = .734$ and $r = .999$ (p for both < 0.0004). Further statistical analysis indicates that there is no significant correlation between the variation in oxygen consumption and either the time between the beginning of the study and the second determination or the total time separating both determinations. Therefore the factor of time as a variant may, within the given limits, be neglected. Since it is necessary to expedite the procedure in cardiacs, only one control determination of cardiac output was

fore that if the oxygen consumption following injection of the drug does not vary from the control value by more than -18 to $+12$ cc. any cardiac output change greater than 9 per cent of the control measurement is due to the action of the drug.

TABLE II
ANALYSIS OF DIFFERENCES BETWEEN TWO SUCCESSIVE MEASUREMENTS OF CARDIAC OUTPUT IN TWENTY CONTROL PATIENTS NOT RECEIVING MEDICATION

	Mean Difference	Range
Cardiac output in per cent of first determination	4.8	-9.0 to +9.2
Oxygen consumption in cc./min./M. ² body surface	7.0	-18 to +12
Arteriovenous difference in volume per cent.	0.2	-0.3 to +0.5
Heart rate in beats per minute	2.0	-6 to +4

The range within which blood pressure measurements varied during the catheterization procedure is presented in Table III. To obtain these data an analysis was made of the control periods of twenty-three cardiac patients who subsequently received digoxin and in whom pulmonary artery, right ventricular and peripheral arterial pressures were repeatedly measured. The period of control observation aver-

aged thirty-two minutes, and the number of observations averaged three per patient. From this table it is evident that variations in pressures as measured by this technic are minimal in the right heart and somewhat larger in the peripheral artery.

TABLE III
ANALYSIS OF DIFFERENCES BETWEEN REPEATED CONTROL MEASUREMENTS OF BLOOD PRESSURES IN A GROUP OF TWENTY-THREE CARDIAC PATIENTS

	Mean Difference	Range
Arterial blood pressures in mm. Hg		
Systolic	11 1	-16 to +29
Diastolic	5.8	-6 to +13
Mean	9 3	-12 to +18
Pulmonary arterial pressures in mm. Hg		
Systolic	1 9	-4 to +5
Diastolic	1 5	-4 to +1
Mean	1.9	-5 to +5
Right ventricular end diastolic pressure in mm. Hg.	1 4	-2 to +4

Average time duration of control period = thirty-two minutes.

Average number of determinations in each patient = three.

The range of variation in these control studies (Tables II and III) is considerably less than in those previously published.¹ This difference may be partially accounted for by an increased experience in use of the technic in cardiac patients and also by the fact that during the period of observation no other procedure intervened between the measurements. In the previously reported "control" series positive pressure breathing was given between measurements.

The stable state of the patient in these studies, as indicated by the aforementioned data, considerably adds to the validity of the changes observed following drug administration.

The upper limit of normal pressure values used in this laboratory are as follows: Pulmonary artery and right ventricular systolic pressure = 30 mm. Hg, pulmonary artery diastolic pressure = 10 mm. Hg, pulmonary artery mean pressure = 15 mm. Hg, right ventricular end diastolic pressure = 5.0 mm. Hg. The range of variation in cardiac output among normal subjects, in L./min./sq. m. body surface area is between 2.70 and 3.50.

RESULTS

The first three patients listed in Tables IV and VIIA had marked systemic hypertension and clinical manifestations of simple left ventricular failure. Clinically and physiologically the first patient (P. A.) showed the least degree of failure while the other two had signs of more advanced hypertensive disease. The control pulmonary artery systolic, diastolic and mean pressures of all were elevated. (Table IV.) The end diastolic pressure of the right ventricle however was normal, indicating a normal right auricular and peripheral venous pressure. The cardiac output was normal in one patient (P. A.), low normal in a second (J. B.) and reduced in the third (G. R.). Peripheral resistance was increased in all three patients, and the total and plasma blood volumes slightly increased in all three.

After administration of digoxin all three patients had a marked decrease in the lesser circulation hypertension. It is noteworthy that the end diastolic pressure in the right ventricle did not change. In each of these three patients the cardiac output rose 36 per cent, 22 per cent and 77 per cent, respectively, and the stroke volume increased markedly, 26 per cent, 53 per cent and 128, respectively. There was no consistent change in arterial blood pressures, one patient (P. A.) showing no change, the second (J. B.) a rise in systolic and mean pressures and a third (G. R.) a rise in systolic with a fall in diastolic and no change in the mean pressure. The peripheral resistance was reduced in all three patients. One patient (P. A.) showed no change in rate, a second patient (J. B.) a minimal slowing and the third patient (G. R.) showed a moderate slowing of the heart rate. Figure 1, showing the effect of digoxin in the patient, J. B., is illustrative of all three cases.

A fourth patient (T. B.), Tables IV, VIIA and Figure 2, had both hypertensive and arteriosclerotic heart disease and an old myocardial infarct. He presented the clinical picture of the previous three patients

and, in addition to the lesser circulation hypertension, had a very low cardiac output and stroke volume and a greater increase in total blood volume than the previous patients. Following digoxin this patient also exhibited a fall in the pulmonary pressures

output and stroke volume. It must be emphasized that with aortic insufficiency this stroke volume is merely an estimation, and the regurgitation *per se* probably plays a role in lowering the effective cardiac output. The typical pressure abnormalities

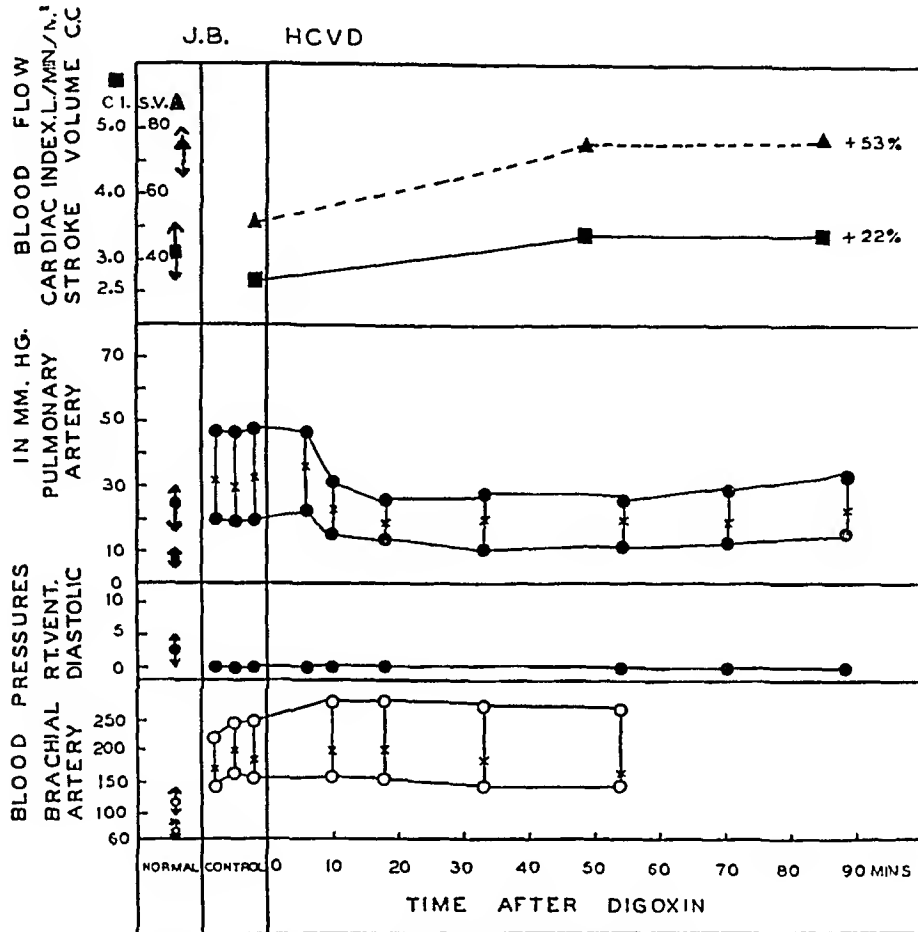


FIG. 1. The effect of intravenous digoxin in a case of left ventricular failure. Closed triangles = stroke volume; closed squares = cardiac index; closed circles = pulmonary artery systolic and diastolic, and right ventricular end diastolic pressures; open circles = brachial artery systolic and diastolic pressures; cross marks = mean pressures. The normal mean values and approximate range of variation are plotted in the first vertical column. Note (1) the increase in stroke volume and cardiac output accompanied by a fall to normal of the elevated pulmonary artery pressures, following administration of the drug, (2) the absence of change in the right ventricular end diastolic pressure and (3) the brachial artery pulse pressure increase.

from hypertensive to normal levels but responded with a smaller increase in cardiac output (12 per cent) and stroke volume (32 per cent). There was no change in arterial blood pressure, peripheral resistance or heart rate. Again the end diastolic pressure in the right ventricle was unaltered.

The fifth patient (R. M.), Tables IV, VIIA and Figure 3, with rheumatic heart disease, mitral stenosis and insufficiency and aortic insufficiency, had a very low cardiac

output and stroke volume. The blood volume was normal and peripheral resistance increased. After digoxin there was a marked increase in cardiac output and stroke volume (47 per cent and 83 per cent, respectively) and a fall to normal of the elevated pulmonary artery pressures. There was no change in right ventricular end diastolic pressure or in arterial blood pressures. There was a fall in peripheral resistance and the heart rate was definitely slowed.

TABLE IV

EFFECT OF INTRAVENOUS DIGOXIN ON BLOOD PRESSURES, CARDIAC OUTPUT, STROKE VOLUME AND HEART RATE IN FIVE PATIENTS WITH LEFT-SIDED HEART FAILURE

Case	Time (min.)	Brachial Artery (mm. Hg)		Pulmonary Artery (mm. Hg)		Right Ventricle (mm. Hg)	Cardiac Output (L./min.)	Stroke Volume (cc.)	Heart Rate (Beats min.)
		s/d	m	s/d	m				
P. A., male, fifty-eight years old; B.S.A. 1.91; HCVD, EH, NSR, PND, IIC	Control	200/100	144	75
		210/99	145	36/16	28	83
		194/94	132	34/12	25	6.78	87	78
		199/99	140	33/12	24	33/5	6.82	88	78
	7*	204/101	142	32/11	24	75
	13	8.56	110	78
	14	212/98	141	26/12	19	78
	27	212/97	142	30/11	22	28/5	75
	36	202/90	133	29/9	21	28/5	77
	48	206/90	133	28/9	20	68
	58	214/94	138	26/9	18
	63	8.24	110	75
	67	210/92	137	25/8	17	75
	85	217/99	139	25/11	17	26/6	75
J. B., male, thirty-one years old; B.S.A. 2.0; HCVD, EH, NSR gallop, PND, IVD, arteriolar nephrosclerosis with uremia and anemia; hypertensive retinopathy and encephalopathy	Control	219/146	172	47/20	32	47/-3	100
		244/156	189	47/19	30	47/-2	100
		247/148	185	48/20	33	48/-1	5.59	53	104
	6*	47/23	36	47/-2	93
	10	276/159	199	32/15	23	30/0	88
	18	278/154	201	26/12	19	28/0	88
	33	268/145	183	28/11	20	88
	48	6.76	77	88
	54	265/144	162	26/12	20	26/-1	88
	70	29/13	19	30/0	86
	84	6.83	79	86
	88	33/16	23	30/0	86
	95	164	28/-2	93
G. R., male, fifty-four years old; B.S.A. 1.78; HCVD, EH, NST gallop, PND, IVD, hypertensive retinopathy	Control	197/128	152	60/43	48	60/3	120
		215/144	166	50	3.92	33	120
		203/138	158	...	53	120
	23*	5.35	54	100
	28	224/115	155	48/16	30	48/3	100
	38	221/115	153	44/15	25	44/2	100
	70	202/100	138	37/13	21	37/2	93
	78	6.95	75	93
T. B., male, fifty-nine years old; B.S.A. 1.93; HCVD, ASHD, EH, CS, MF, old infarct, NSR, LBBB, gallop, PND, angina, IIC	Control	148/85	106	40/22	26	40/1	4.10	53	78
		137/80	102	40/20	26	78
	9*	149/85	107	33/17	21	71
	14	146/80	102	30/14	18	30/2	65
	20	4.55	70	65
	25	151/83	105	29/17	21	65
	30	144/78	99	27/10	15	27/2	65
	35	4.39	68	65
	42	154/86	103	25/13	17	25/1	68
	52	140/79	96	23/11	15	23/1	71
	69	146/82	101	24/11	15	24/2	65

TABLE IV (Continued)

Case	Time (min.)	Brachial Artery (mm. Hg)		Pulmonary Artery (mm. Hg)		Right Ventricle (mm. Hg)	Cardiac Output (L./min.)	Stroke Volume (cc.)	Heart Rate (Beats min.)
		s/d	m	s/d	m				
R. M., male, forty-nine years old; B.S.A. 1.33; RHD, EH, MS, MI, AI, NSR, LBBB, gallop, PND, IIIC	Control	144/60	100	56/31	39	56/3	2.13	23	94
	6†	143/50	93	49/19	30	49/0	78
	18	154/51	98	28/10	17	28/0	75
	27	150/47	94	20/7	9	20/0	75
	33	2.98	40	75
	38	162/52	100	20/9	13	20/0	75
	47	153/48	93	18/6	9	18/0	75
	54	3.13	42	75
	60	156/48	94	19/8	11	19/0	75

* Time after start of injection of 1.5 mg. digoxin.

† Time after start of injection of 1.0 mg. digoxin.

s = systolic. d = diastolic. m = mean.

B.S.A. = Body surface area in square meters.

ASHD = Arteriosclerotic heart disease.

HCVD = Hypertensive cardiovascular disease.

RHD = Rheumatic heart disease.

AI = Aortic insufficiency.

CS = Coronary sclerosis.

EH = Enlarged heart.

MI = Mitral insufficiency.

MF = Myocardial fibrosis.

MS = Mitral stenosis.

PND = Paroxysmal nocturnal dyspnea.

NSR = Normal sinus rhythm.

LBBB = Left bundle branch block

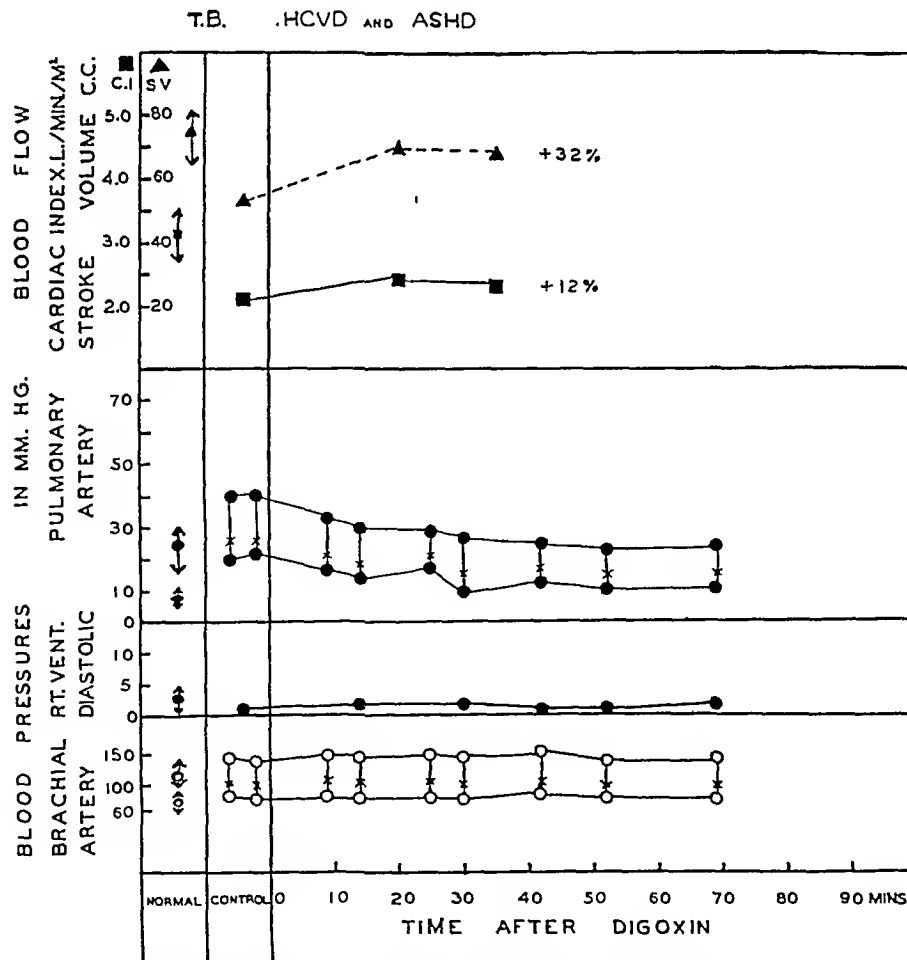


FIG. 2. The effect of digoxin in left ventricular failure. (For symbols see Figure 1.) Note (1) the initially low cardiac output, (2) the smaller increase in cardiac output as compared to the other cases, (3) marked pressure drop in the pulmonary artery, (4) no change in right ventricular end diastolic pressure and (5) insignificant changes in brachial artery pulse pressure.

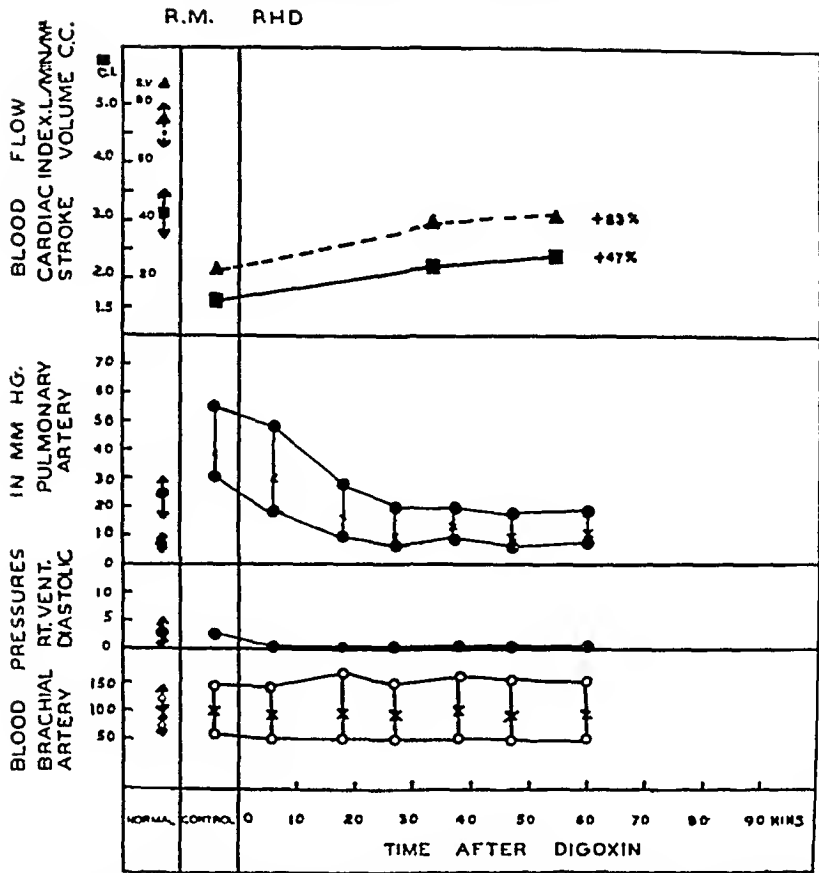


FIG. 3. The effect of digoxin in left ventricular failure. (For symbols see Figure 1.) The hemodynamic response is identical with that in the previous cases (Figs. 1 and 2).

TABLE V
EFFECT OF QUINIDINE SULFATE ON BLOOD PRESSURES, CARDIAC OUTPUT, STROKE VOLUME AND HEART RATE IN A FULLY DIGITALIZED PATIENT WITH RHEUMATIC HEART DISEASE AND LEFT-SIDED FAILURE

Case	Time (min.)	Brachial Artery (mm. Hg)		Pulmonary Artery (mm. Hg)		Right Ventricle (mm. Hg)	Cardiac Output (L./min.)	Stroke Volume (cc.)	Heart Rate (Beats/min.)
		s/d	m	s/d	m				
J. L., male, sixty-three years old; B.S.A. 1.43; RHD, EH, MS, MI, AI, NSR, IHC	Control	147/77	106	40/14	23	40/2	2.93	43	68
		150/79	109						68
	29*	134/70	97						75
	54	109/56	73						75
	62	101/55	74	30/7	15				75
	77						4.02	54	75
	92	99/53	72	31/9	16				75
	97	102/56	75			26/0			75
	117						3.50	47	75
	132	109/59	82			25/2			75

* Time after 0.8 Gm. quinidine sulfate by mouth.
s = systolic, d = diastolic, m = mean.
RHD = Rheumatic heart disease.
AI = Aortic insufficiency.

EH = Enlarged heart.
MI = Mitral insufficiency.
MS = Mitral stenosis.
NSR = Normal sinus rhythm.

In summary, these five patients with left-sided heart failure responded to digoxin in exactly the same manner; without change in right heart end diastolic pressure the cardiac output and stroke volume rose and the pulmonary hypertension was di-

normal of the elevated pulmonary artery pressures. The heart rate did not vary significantly.

In contrast to these patients is a patient with chronic cor pulmonale in congestive failure who was also treated with digoxin.

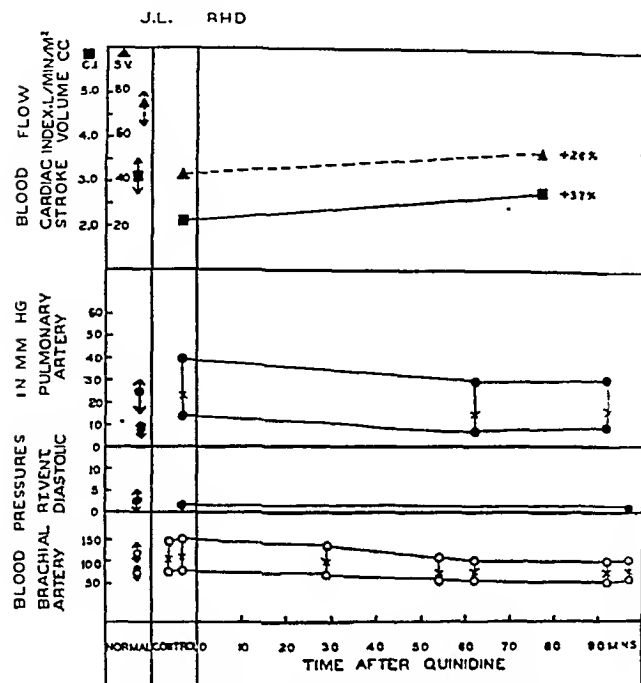


FIG. 4. The effect of quinidine sulfate in left ventricular failure. (For symbols see Figure 1.) Note that following a decrease in peripheral resistance induced by quinidine, there was (1) a rise in stroke volume and cardiac output, (2) a fall in pulmonary artery pressures and (3) no change in right ventricular end diastolic pressure.

minished. The apical diastolic gallop found in four patients disappeared after digoxin. In two patients the heart rate fell significantly. The peripheral resistance was decreased in four.

The data in a patient with left-sided heart failure who received quinidine is presented in Tables v, viii and Figure 4. This patient with rheumatic heart disease was digitalized and symptom-free on bed rest but nevertheless had pulmonary hypertension and a low cardiac output and stroke volume. There was a normal end diastolic pressure in the right ventricle, a normal blood volume and increased peripheral resistance. Quinidine, 0.8 Gm. orally, produced a marked fall in arterial blood pressure, a fall in peripheral resistance and a rise of 37 per cent in cardiac output and 26 per cent in stroke volume, with a return to

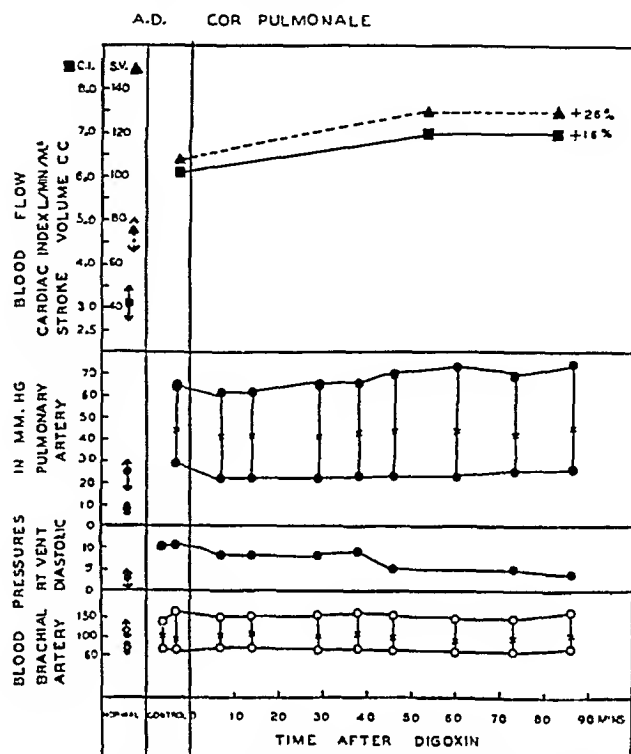


FIG. 5. The effect of digoxin in right heart failure due to cor pulmonale. (For symbols see Figure 1.) Note that (1) the initially elevated cardiac output rose considerably after digoxin, (2) the elevated right ventricular end diastolic pressure returned to normal and (3) with the increase in stroke volume the pulmonary artery systolic pressure rose, a response different from the pulmonary artery response in patients in left ventricular failure.

(Tables vi, viii and Fig. 5.) The elevated pulmonary artery pressures were accompanied by an elevated end diastolic pressure in the right ventricle as would be expected in congestive right-sided heart failure. Clinically the patient had an enlarged liver and peripheral edema. The elevated cardiac output, polycythemia with increased total blood and plasma volumes and arterial blood oxygen unsaturation complete the classical picture of cor pulmonale in cardiac failure.

Following injection of 1.5 mg. of digoxin there was an increase of 16 per cent in cardiac output and of 26 per cent in stroke volume. (Tables vi and viii.) The response of the pulmonary circulation to this rise in

output was in sharp contrast to that demonstrated by the patients with left heart failure. The elevated right ventricular end diastolic pressure returned to normal with the increase in stroke volume. The pulmonary artery and right ventricular systolic

one-tenth the resistance in the systemic circulation. Furthermore, the deformability of the pulmonary system is such that it can accommodate a three-fold cardiac output increase without pressure changes in the pulmonary artery.^{5,6}

TABLE VI

EFFECT OF DIGOXIN ON BLOOD PRESSURES, CARDIAC OUTPUT, STROKE VOLUME AND HEART RATE IN A PATIENT WITH COR PULMONALE AND CONGESTIVE HEART FAILURE

Case	Time (min.)	Brachial Artery (mm. Hg)		Pulmonary Artery (mm. Hg)		Right Ventricle (mm. Hg)	Cardiac Output (L./min.)	Stroke Volume (cc.)	Heart Rate (Beats min.)
		<i>s/d</i>	<i>m</i>	<i>s/d</i>	<i>m</i>	<i>s/d</i>			
A. D., female, fifty-five years old; B.S.A. 1.65; cor pulmonale. EH, NSR, chronic bronchial asthma; mild emphysema	Control	140/75	103	63/29	44	63/10	97
		160/71	95	62/11	10.0	103	97
	7*	147/77	106	62/22	41	62/8	88
	14	150/74	107	62/22	41	62/8	85
	29	152/72	104	65/22	41	65/8	88
	38	161/74	110	66/23	43	66/9	88
	46	152/71	102	69/23	44	69/5	88
	53	11.6	130	88
	60	144/68	96	73/23	44	88
	73	145/67	99	69/25	42	69/5	88
	82	11.6	130	88
	86	159/75	108	74/26	45	74/4	88

* Time after start of injection of 1.5 mg. digoxin.
s = systolic. *d* = diastolic. *m* = mean.

EH = Enlarged heart.
NSR = Normal sinus rhythm.

pressures, however, showed an increase after digoxin. The systolic pressure in the pulmonary artery and right ventricle rose from 63 to 74 mm. Hg without any striking change in pulmonary artery diastolic or mean pressures. Changes were minimal in peripheral resistance and arterial pressures. The heart rate slowed slightly.

COMMENTS

The feature held to be characteristic of left heart failure is pulmonary congestion. In order to evaluate the various mechanisms concerned in the production of such congestion a comment on the known characteristics of pulmonary circulation in man becomes necessary.

The pulmonary vascular system is characterized by low resistance because of easy deformability and, therefore, increased distensibility. Measurement of pressures and flow indicates that in the normal pulmonary circulation the resistance at rest is about

In any discussion of the pulmonary vascular system not only its inherent characteristics must be considered but also the influence of left auricular pressure variations must be evaluated. There are anatomic and physiologic differences between the two sides of the heart. As Cournand⁷ originally commented, "There are differences between (a) the two auricles, the left auricular wall being thicker than the right; (b) their venous reservoir, the four pulmonary veins being shorter and their diameter smaller than the superior or inferior vena cava; and (c) both ventricles, the muscular development of the left ventricle being much greater than the right. These anatomic differences suggest that the left auricle is less deformable than the right, that its venous reservoir has a smaller capacity, and finally that effects of muscular activity of the left ventricle upon volume and tension in the left auricle may be more pronounced than similar activity of the right ventricle

TABLE VII

PHYSIOLOGIC DATA CONCERNING CARDIAC OUTPUT AND BLOOD VOLUME IN (1) FIVE PATIENTS WITH LEFT-SIDED HEART FAILURE TREATED WITH DIGOXIN, (2) ONE PATIENT WITH LEFT-SIDED FAILURE TREATED WITH QUINIDINE AND (3) ONE PATIENT WITH COR PULMONALE TREATED WITH DIGOXIN

Case	Time (min.)	Cardiac Index (L./min./ M. ² BSA)	Oxygen Consump- tion (cc./min./ M. ² BSA)	AV Oxygen Differ- ence (vol. %)	Arterial			Periph- eral Resist- ance (dynes sec. cm. ⁻⁵)	Blood Volume§		
					Blood Content (vol. %)	Oxygen Capacity (vol. %)	Satura- tion (%)		TBV** (cc./M. ²)	PV†† BSA)	Hemato- crit (%)
(1)											
P. A.	Control	3.55	160	4.5	16.3	1555	2870	1810	37
		3.63	160	4.4	16.2	16.6	97.5	1600			
	13*	4.47	161	3.6	15.4	16.2	96.0	1315			
	63	4.45	160	3.6	15.4	16.4	96.0	1330			
J. B.	Control	2.77	177	6.4	12.5	14.8	86.0	2650	3085	2063	33
	48*	3.35	164	4.9	11.9	13.6	89.0	1915			
	84	3.38	162	4.8	11.6	13.3	89.0	1920			
G. R.	Control	2.20	154	7.0	16.7	17.6	95.0	3490	3138	1740	45
	23*	3.00	154	5.2	16.6	2555			
	78	3.91	152	3.9	15.9	1590			
T. B.	Control	2.14	147	6.9	19.9	20.6	97.5	2020	3680	1928	48
	20*	2.37	142	6.0	18.7	20.6	91.6	1840			
	35	2.29	128	5.6	18.6	1880			
R. M.	Control	1.60	155	9.7	17.5	19.1	93.0	3760	2670	1465	45
	33†	2.23	156	7.0	17.0	17.9	96.0	2780			
	54	2.35	160	6.8	16.7	2400			
(2)											
J. L.	Control	2.05	121	5.9	18.8	19.8	95.9	2980	2790	1500	45
	77‡	2.81	127	4.5	18.3	19.7	93.8	1500			
	117	2.45	127	5.2	18.1	19.0	96.0	1875			
(3)											
A. D.	Control	6.06	170	2.8	12.3	20.5	60.0	720	6060	2043	66
	53*	7.05	176	2.5	11.1	20.4	65.0	625			
	82	7.04	162	2.3	12.3	20.3	61.0	725			

* Time after start of injection of 1.5 mg. digoxin.

† Time after start of injection of 1.0 mg. digoxin.

‡ Time after 0.8 Gm. quinidine sulfate by mouth.

§ Predicted Values: Total Blood Plasma Hematocrit

Male.....	2900	1600	45
Female.....	2670	1600	40

** TBV = Total blood volume.

†† PV = Plasma volume.

upon volume and tension in the right auricle." There is increasing evidence that mean pressure in the left auricle is normally higher than in the right auricle and that the distensibility of the left ventricle, left auricle and pulmonary veins is less than it is in similar structures of the right heart. This evidence stems from direct measurements of left auricular pressure curves in man,⁷ and a similar conclusion is reached from the indirect measurements reported by Dexter⁸ and Werkö.⁹ The characteristic difference between the two auricles has recently been confirmed in dogs by Opdyke et al.¹⁰

It follows from these studies that for the same volume change there will be a greater pressure change in the left heart and pulmonary veins than would be found in the right heart and systemic veins during any one cardiac cycle. This in turn probably favors the onset of pulmonary congestion earlier than systemic congestion for a comparable increase in residual volume of the two ventricles. Furthermore, the mean pressure difference between the pulmonary artery and the left auricle in normal subjects is very small, probably less than 10 mm. Hg. As the arterioles and precapillaries have very little smooth muscle most of the pressure drop must be between the main pulmonary artery and its branches. Conversely, with resistance in pulmonary arterioles unchanged any increase in pressure in the pulmonary veins must easily raise the pressure in the capillaries, precapillaries and arterioles and eventually effect a rise in the mean pulmonary arterial pressure.

Failure of the left heart results in an increase in the residual blood volume in the left ventricle and auricle and hence produces an increase in pressure in the latter chamber which is easily reflected throughout the pulmonary vascular tree producing pulmonary hypertension. Clinically this is expressed as pulmonary congestion.

It is quite obvious that pulmonary hypertension may also be a manifestation of abnormalities of the pulmonary vascular bed

resulting from a diminution in capacity of the arteriolar and capillary system.

The five patients treated with digoxin clinically had evidence of left-sided failure. In four of these patients failure of the left ventricle to empty adequately resulted in an increase in residual blood in the left ventricle with a subsequent increase in filling pressure. In one patient (R. M.) the mitral stenosis itself might have produced elevation of the pressure in the left auricle for mechanical reasons. However, aortic insufficiency could have been the cause of left ventricular failure and of the rise in left auricular pressure.

In all these patients an increased stroke volume occurred concomitantly with a reduction in the pulmonary hypertension following digoxin administration. This suggests a more adequate emptying of the left ventricle and a reduction in the residual blood volume of this chamber and left auricle. The increased systemic flow obviously results in an increased return of blood to the right heart. This was accomplished, however, without detectable change in the end diastolic pressure of the right ventricle. This is the characteristic response of a normally functioning right heart in which large volume changes are associated with minimal filling pressure increase.^{10,11} Since the pulmonary pressures of the patient with rheumatic heart disease, mitral stenosis and aortic insufficiency (R. M.) fell to normal after administration of digoxin, it is difficult to escape the conclusion that his pulmonary hypertension was the result of failure of the left ventricle to empty adequately rather than the result of mechanical obstruction at the mitral valve.

In the patient (J. L.) treated with quinidine, who also had mitral stenosis and aortic insufficiency, the pulmonary artery pressures also returned to normal levels. This suggests that left ventricular failure rather than mechanical obstruction at the mitral valve produced pulmonary hypertension. With the peripheral vasodilatation produced by quinidine the left ventricle was

able to empty more completely, thus reducing the pressures in the lesser circulation. This is further evidence of the importance of the action of the left ventricle upon the pulmonary circulation.

An entirely different physiologic situation existed in the patient with chronic cor pulmonale and pulmonary hypertension. In this instance reduction in pulmonary arteriolar caliber was the underlying cause of hypertension of the lesser circulation as was suggested by extensive pulmonary function studies. The right heart, working against markedly increased resistance, was failing to empty itself as was evidenced by the increase in end diastolic pressure. The left heart, however, was presumably not failing to empty itself efficiently although the assumption of normal left auricular pressure cannot be proved.

After digoxin better emptying of the right ventricle reduced the residual volume and filling pressure but caused an increase in the pulmonary artery systolic pressure. This suggests that when an increase in blood flow takes place within a pulmonary vascular bed with a pathologically restricted capacity it cannot be accommodated without a rise in pressure in the pulmonary artery. A similar effect upon the pulmonary arterial pressure in patients with a restricted pulmonary vascular bed has been observed when cardiac output is increased following exercise.^{5,6}

It should be emphasized that all the hemodynamic changes produced by the drugs here noted were only followed for a period of one and one-half to two hours. These acute changes do not necessarily reflect the final or optimal effect of the medication and any conclusions as to long term results are not justified.

Mode of Action of Digoxin. In recent attempts to delineate more precisely the mode of action of digitalis preparations in the human circulation a peripheral venous action has been postulated.¹² This assumption was based on material in which the right atrial mean pressure was used as an indication of the filling pressure of the right

heart. Since in the present study there was no change after digoxin in the right ventricular end diastolic pressure, which reflects central venous pressures but is a better index of the filling pressure of the right heart than the mean auricular pressure, this assumption of a predominantly venous action of digoxin is not tenable in cases of left ventricular failure. The improvement in stroke volume and reduction in pulmonary congestion on the other hand suggest a predominantly myocardial effect of the drug. It would seem unreasonable to postulate instead a specific isolated effect of the drug on the pulmonary venous bed. With no change in heart rate in two of the five patients studied it is apparent that this myocardial action is, at least in some cases, independent of a change in the heart rate.

The action of digitalis bodies upon the peripheral arteriolar bed has also been much discussed and in man the effect upon systemic blood pressure has been reported as variable.¹³⁻¹⁵ Analysis of changes in arterial blood pressure following intravenous digoxin in this group of patients contributes additional information to solution of this problem. As seen in Figure 6 the five patients with left ventricular failure showed either a small fall or no change in mean arterial pressure as the cardiac output rose in varying degrees. These changes indicate a moderate reduction in peripheral resistance. They are in sharp contrast to the effect of a similar dose of the drug in two subjects with normal hearts¹⁶ plotted on the same graph. In the latter cases a fall in cardiac output was accompanied by no change in arterial mean pressure in one subject and a marked rise in the other, indicating in both cases an increase in peripheral resistance. A similar response has been observed in a larger group of cardiac patients with enlarged hearts but no evidence of failure.¹⁶ This vasoconstrictor effect has also been observed in animals given large doses of digitalis.¹³⁻¹⁴

In the group of patients with left ventricular failure it is unlikely that a primary vasodilator effect alone could account for

the increase in cardiac output. This is made evident by a comparison of blood pressure changes in those given digoxin with those seen in three patients with cardiac failure treated with quinidine, a drug known to produce vasodilatation.^{1,17} As can be seen

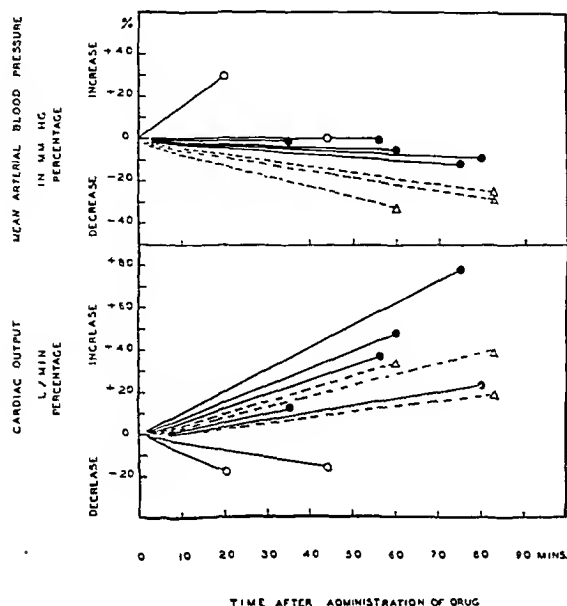


FIG. 6. Simultaneous brachial artery mean blood pressures and cardiac output changes following digoxin and quinidine. Open circles = patients with normal circulation receiving intravenous digoxin; closed circles = patients in left ventricular failure receiving intravenous digoxin; open triangles = patients in cardiac failure receiving 0.8 Gm. quinidine sulfate.

in Figure 6 the mean arterial pressure fall was much greater in the patients given quinidine for an increase in cardiac output which was usually smaller than in the patients given digoxin.

All these data suggest that the changes in peripheral vascular resistance after digoxin represent reflex alterations in dynamics secondary to the increase in stroke volume rather than a primary effect upon the arterioles. This homeostatic response could be mediated through the moderator nerves (aortic body and carotid sinus) or through effects upon the central vasomotor center. One cannot rule out an accompanying vasoconstrictor effect in these cardiac patients but if this antagonistic effect is present it must have been overcome by reflex vasodilatation.

SUMMARY AND CONCLUSIONS

1. The early effect of intravenous digoxin is studied by the cardiac catheterization procedure in five patients with left-sided heart failure.

2. Digoxin produced a significant rise in cardiac output and stroke volume accompanied by a decrease in pulmonary arterial pressure in each of these five patients. These changes were effected without alteration in the right ventricle end diastolic pressure and therefore cannot be ascribed to an action of the drug upon the systemic venous system but rather are interpreted as an action of digoxin upon the myocardium.

3. Similar changes in cardiac output, stroke volume and pulmonary arterial pressure were observed in a patient with left ventricular failure after the peripheral resistance had been lowered by quinidine.

4. The tentative conclusion can therefore be reached that regardless of the cause of the stroke volume increase—myocardial action or a reduction in peripheral vascular resistance—the pulmonary congestion in six patients with left ventricular failure was relieved as a result of more satisfactory emptying of the left ventricle.

5. The conclusion that ventricular ejection and ventricular filling are mutually dependent upon the functional state of the myocardium seems inescapable.

6. As a contrast to the patients with left ventricular failure the effect of digoxin upon pulmonary blood flow and blood pressures in a patient with cor pulmonale is presented.

Acknowledgments. We gratefully acknowledge the assistance of Mrs. Marianne Lester, Blanche Spierito and Dorothy Allen, and Drs. Herbert M. Weiner, Robert E. Johnson and Charles A. Webster.

REFERENCES

1. FERRER, M. I., HARVEY, R. M., WERKO, L., DRESDALE, D. T., COUNAND, A. and RICHARDS, D. W., JR. Some effects of quinidine sulfate on the heart and circulation in man. *Am. Heart J.*, 36: 816, 1948.
2. COUNAND, A. and RANGES, H. A. Catheterization of the right auricle in man. *Proc. Soc. Exper. Biol. & Med.*, 46: 462, 1941.

3. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. DEF. and Richards, D. W., JR. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. *J. Clin. Investigation*, 24: 106, 1945.
4. Noble, R. P. and Gregersen, M. I. Blood volume in clinical shock. I. Mixing time and disappearance rate of T-1824 in normal subjects and in patients in shock; determinations of plasma volume in man from ten minute sample. *J. Clin. Investigation*, 25: 158, 1946.
5. Hickam, J. B. and Cargill, W. H. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and patients with cardiovascular disease and pulmonary emphysema. *J. Clin. Investigation*, 27: 10, 1948.
6. Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M. and Cournand, A. Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. *Am. J. Physiol.*, 152: 372, 1948.
7. Cournand, A., Motley, H. L., Himmelstein, A., Dresdale, D. T. and Baldwin, J. Recording of blood pressure from the left auricle and pulmonary veins in human subjects with interauricular septal defect. *Am. J. Physiol.*, 150: 267, 1947.
8. Hellem, H. K., Haynes, F. W., Dexter, L. and Kinney, T. D. Pulmonary capillary pressure in animals, estimated by venous and arterial catheterization. *Am. J. Physiol.*, 155: 98, 1948.
9. Werkö, L. Personal communication.
10. Opdyke, D. F., Duomarco, J., Dillon, W. H., Schreiber, H., Little, R. C. and Seely, R. D. Study of simultaneous right and left atrial pressure pulses under normal and experimentally altered conditions. *Am. J. Physiol.*, 154: 258, 1948.
11. Cournand, A., Motley, H. L., Werkö, L. and Richards, D. W., JR. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *Am. J. Physiol.*, 152: 162, 1948.
12. McMichael, John. Circulatory failure studied by means of venous catheterization. *Advances in Internal Medicine*. P. 77. New York, 1947. Interscience Publishers, Inc.
13. Sollman, T. A Manual of Pharmacology. P. 525. Philadelphia, 1934. W. B. Saunders Co.
14. Goodman, L. and Gilman, A. The Pharmacological Basis of Therapeutics. P. 515. New York, 1941. The MacMillan Co.
15. Movitt, E. R. Digitalis and Other Cardiotonic Drugs. P. 20. New York, 1946. Oxford University Press.
16. To be reported.
17. Hiatt, E. P. Effects of repeated oral doses of quinine and quinidine on the blood pressure and renal circulation of dogs with experimental neurogenic hypertension. *Am. J. Physiol.*, 155: 114, 1948.

Coarctation of the Aorta^{*}

Photo-electric Plethysmography and Direct Arterial Blood Pressure Measurement as an Aid in Diagnosis

MELVIN L. GOLDMAN, M.D. and HENRY A. SCHROEDER, M.D.

St. Louis, Missouri

THE clinical diagnosis of coarctation of the aorta can be made without difficulty when there is enough constriction of the aorta to cause collateral circulation to become well established. However, the degree of constriction may vary from a slight indentation to practically complete obliteration. The site of coarctation may also vary and anomalies of the great vessels may be present. Therefore, it is advantageous to establish the site and degree of the constriction in order to decide whether or not the condition can be corrected surgically and whether operation is likely to be hazardous.

The purpose of this report is to present the combination of two well established methods for the study of blood flow and blood pressure, namely, photo-electric plethysmography and direct measurements of arterial blood pressure as an aid to the diagnosis and location of coarctation of the aorta. By these means the relative blood flow of peripheral parts can be estimated and accurate blood pressure in an extremity can be measured.

METHOD

Two photo-electric plethysmographs were used to compare simultaneously the relative blood flow in the ear lobes, fingers, scrotum or toes. The photo-electric plethysmograph consisted of a 2.2 volt pencil flashlight bulb as a light source and a photo-electric cell (Cetron 22-A. B.) in a small metal holder

which could be adjusted to fit around a peripheral part. Variations in the density of the part were amplified and by means of a rapidly moving galvanometer (Sanborn cardiette) were recorded on a kymographic camera, the speed of which could be varied from 0.2 mm. per second to 75 mm. per second. Changes both in amplitude of pulse and opacity of the part were recorded semi-quantitatively. A Hamilton optical manometer recorded blood pressure simultaneously, as well as the contour of the pulse. Fourteen cases of coarctation of the aorta were studied; one patient (J. F.) had undergone surgical correction by an end-to-end anastomosis of the aorta; another (W. W.) was studied before and after operative correction of the defect. All measurements were made in the horizontal position and in a constant room temperature of 80°f.

RESULTS

The systolic blood pressure in the femoral artery in normal subjects is approximately 20 mm. Hg higher than in the axillary, the diastolic being about the same when measured by direct arterial puncture.¹ Blood flow as indicated by the amplitude of the pulse wave is approximately the same or slightly less in the scrotum as compared with the ear lobe, or the toes as compared with the fingers. A comparison for absolute values between subjects cannot be made because of variations in the thickness of the peripheral parts.

^{*} From the Department of Internal Medicine and the Oscar Johnson Institute, Washington University School of Medicine, and the Barnes Hospital, St. Louis, Mo., under a grant-in-aid from the U. S. Public Health Service.

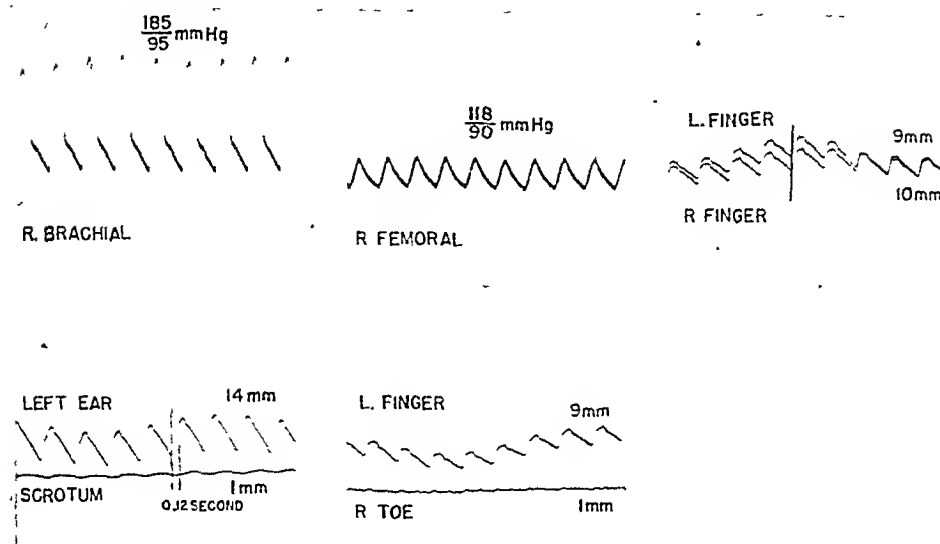


FIG. 1. Case IV, L. H. Photographic records of arterial pressure in the brachial and femoral arteries and of photoelectric plethysmograms in the fingers, toes, ear and scrotum. Note the change in contour of the femoral pulse. There is no difference in the timing of the pulses in the two fingers but a delay of 0.12 seconds between that in the ear and scrotum is evident. Note the abnormally small pulse in the toe. The camera speed was 25 mm. per second.

In a normal man the pulse wave velocity is 5 to 9 meters per second, depending upon the size and elasticity of the particular artery or group of arteries.² The velocity in the aorta is slower than that in peripheral vessels. The time lag between the rise of the pulse waves in the fingers and toes varies from 0.06 to 0.12 seconds. Since the distance between the finger and toe is about 40 per cent of the height, a rough estimate of the velocity of the pulse wave can be made. In four normal young adults this varied from 6.2 to 10 M. per second. The ear to scrotum velocity was much slower owing probably to the diameters and elasticity of the vessels traversed and to the special character of the tissues. (3.2 to 3.5 M. per second assuming a distance of about 20 per cent of the height.)

Comparing the above "normal" findings with those of severe, moderate and sub-clinical coarctation, striking differences were found. Figure 1 shows the results in a patient with severe coarctation (Case IV, Tables I and II.) The significant findings were: (1) a marked diminution in the systolic pressure in the femoral artery (118 mm. Hg) as compared to the brachial artery (185 mm. Hg) while the diastolic pressures were approximately the same;

(2) marked diminution in the amplitude of the pulse wave of the scrotum (1 mm.) as compared to the left ear lobe (14 mm.), and of the toe (1 mm.) as compared to the finger (9 mm.); (3) delay of 0.12 seconds in the rise of the pulse wave of the scrotum as compared to the ear (pulse wave velocity 2.6 M. per second) and (4) equal pulsations in the fingers of the two hands. From these data one can conclude that the coarctation was distal to the origin of the left subclavian artery and was probably of the adult type. The marked diminution of the pulse amplitude in the scrotum and toes is compatible with a severe constriction of the aorta. These findings were in keeping with the clinical signs.

Figure 2 (Case III) represents a case of moderately severe coarctation, with aortic insufficiency probably on the basis of rheumatic heart disease. Photo-electric plethysmography revealed that the amplitude of the pulse of the left ear was 32 mm.; of the right, 7 mm.; of the index finger of the left hand, 31 mm.; of the right, 35 mm.; of the left index finger 32 mm.; of the right second toe, 3.5 mm., with a delay of approximately 0.12 seconds in the pulse wave of the toe. (Velocity 3.8 M. per second.) The amplitude in the left second toe was

9 mm. and in the right, 5 mm. The right brachial blood pressure was 214 mm. Hg systolic and 57 mm. diastolic; the left brachial was 124 mm. systolic and 70 diastolic and the right femoral artery was 87 mm. systolic and 54 diastolic.

because of the presence of hypertension, shortness of stature, hypo-ovarianism and an abnormally short fourth toe.³ The blood pressure in the legs by the auscultatory method using the usual size cuff was found by several observers to be higher than it was

TABLE 1
CLINICAL FINDINGS IN PATIENTS WITH COARCTATION OF THE AORTA

Case No.		Duration of Symp- toms (mo.)	Age When Diag- nosis Was Made	Symptoms and Signs										Pulsations			Evidence of Collateral Circulation							
Sex	Age			Dyspnea	Edema	Fatigue	Palpitation	Precordial Pain	Claudication	Headache	Hypogonadism	Short Stature	Abnormal Digits †	B.M.R. (Per Cent)	Femoral	Popliteal	Dorsalis Pedis	Intercostal Pulsation	Subscapular Pulsations	Deep Epigastric	Notching of Ribs in X-ray	Cardiac Enlargement from X-ray	Aortic Insufficiency	Systolic Murmur
I ♀	22	21	21	+	0	+	0	0	0	0	+	+	-6	Small	Small	Small	+	+	+	0	0	+	+	Normal
II ♀	36	0	36	0	0	0	0	0	0	0	+	+	+7	+	+	+	0	0	0	0	0	0	+	Normal
III ♀ †	8	2	8	+	0	0	0	0	0	0	.	.	+	Small	Small	Small	+	+	+	+	+	+	+	LAD* P-R+
IV ♂	22	5	22	0	0	0	0	0	0	0	0	+	0	...	Small	0	0	+	+	+	+	0	0	+
V ♂	24	3	23	0	0	0	0	0	0	+	0	0	0	...	Small	Small	Small	0	0	0	+	+	0	+
VI ♂	47	7	47	+	0	0	0	+	0	+	0	0	0	+15	Small	Small	Small	+	0	0	0	0	0	+
VII ♂ †	4	0	4	0	0	0	0	0	0	0	0	0	0		Small	0	0	+	+	.	0	0	0	+
VIII ♂ †	14	1	14	+	0	+	0	0	0	0	0	0	+		Small	Small	0	0	0	0	0	0	+	Normal
IX ♀	24	6	24	0	0	0	0	+	+	+	+	+	+8	Small	Small	Small	+	+	+	+	+	0	0	+
X ♀ †	10	1	10	0	0	0	0	0	0	0	0	0	.	+	+	+	0	0	0	0	0	0	+	
XI ♂	15	24	15	0	0	0	0	0	+	0	0	0	+	0	0	0	+	+	+	+	0	+	+	Normal
XII ♂	16	48	16	+	0	+	0	0	+	0	0	0	0	0	0	0	0	0	0	+	0	0	+	LAD*
XIII ♂	31	0	31	+	0	+	0	0	0	0	0	0	0	+	0	0	0	+	+	+	+	0	0	Normal
XIV ♂	26	0	21	+	0	+	0	0	0	0	0	0	+4	+	0	0	0	+	+	+	+	0	0	Normal

* LAD = Left axis deviation.
† Patients of St. Louis Children's Hospital. Case VII has been published.¹⁴
‡ These cases will be discussed in a separate publication.
Table modified after Stewart and Bailey.⁴

These data are compatible with (1) aortic insufficiency, (2) interference in blood flow to the lower extremities, (3) anomalous origin of the left subclavian artery and (4) constriction of the aorta distal to or at the site of origin of the left subclavian artery. The correctness of this interpretation was established at operation which confirmed the location of the coarctation.

Figure 3 (Case II) represents a subclinical case of coarctation. The patient was studied

in the arms. With a large blood pressure cuff (19 cm. wide) the values as reported in Table II were obtained. The amplitude of the pulse wave of the right finger was 3.5 mm. as compared with 2 mm. of the right foot, not a striking difference. However, the direct systolic pressure in the right brachial artery was 193 mm. Hg and the diastolic 116 while that of the right femoral was 162 mm. Hg and the diastolic 107. These findings were interpreted as com-

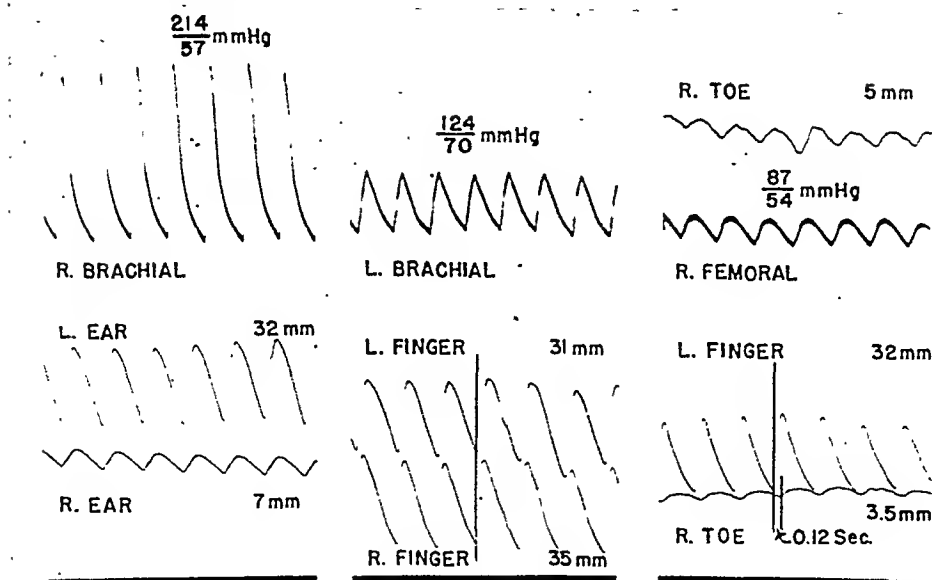


FIG. 2. Case III, N. P. Photographic records of arterial pressure and plethysmograms in an eight year old child with aortic insufficiency and coarctation of the aorta. The left subclavian artery arose at the site of the coarctation. Note the difference in blood pressure between the right and left brachial arteries and the femoral. The plethysmogram of the right second toe was taken simultaneously with the femoral arterial pressure. A large dilated vessel in the neck, which may have been an aneurysm, may account for the difference in pulses between the two ears. The similarity of the amplitude of the pulses in the two fingers is unexplained, but there is a slight delay in the left as compared with the right. In spite of the aortic insufficiency the pulse wave velocity between the finger and toe was prolonged. The camera speed was 25 mm. per second.

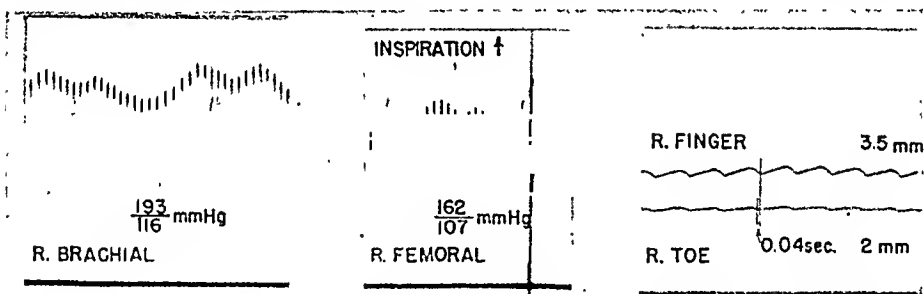


FIG. 3. Case II, O. P. Record reads from right to left; speed of camera 5 mm. per second. The patient exhibited a very slight degree of coarctation of the aorta according to retrograde arteriograms. The systolic pressure in the femoral artery is lower than that in the brachial, but the velocity of the pulse wave from finger to toe, if anything, is elevated. This patient also suffered from arterial hypertension.

patible with a mild coarctation of the aorta and arterial hypertension. The velocity of the pulse wave from finger to toe was 14.5 M. per second which is inconsistent with a coarctation of any pronounced degree. Aortic arteriography confirmed this impression.

The most consistent finding was a lower systolic pressure in the femoral than in the brachial artery. (Table II.) In only one case (W. W.) was there a marked difference in diastolic pressure. This was found in a fifteen year old boy who complained of

intermittent claudication in the legs. He was short in stature. The essential findings (Fig. 4) were: (1) a systolic pressure of 205 mm. Hg in the brachial artery and 75 in the femoral, (2) a diastolic pressure of 92 mm. Hg in the brachial and 50 in the femoral, (3) diminution in the amplitude of the pulse in the left ear as compared to the right, (4) a delay in the appearance of the pulse in the scrotum of 0.18 seconds as compared to the ear (pulse wave velocity of 1.5 M. per second) and (5) absence of

pulsation in the toes. A double peak in the tracing made from the brachial artery was also noticed. These findings were consistent with a severe coarctation. The low amplitude of the pulse in the left ear was assumed to have been the result of retrograde aortic

of constriction as indicated by a lower systolic pressure in the femoral artery. The pulse wave velocity, ear to scrotum, was now 3.3 M. per second and that of the finger to toe 5.3 to 5.9 M. per second (approximately within normal limits).

TABLE II
SPECIAL STUDIES IN PATIENTS WITH COARCTATION OF THE AORTA

Case No	Blood Pressure* (mm. Hg)				Difference in Direct Arterial Blood Pressure Brachial-Femoral (mm. Hg)		Photoelectric Plethysmography (amplitude in mm.)						Pulse Wave Velocity (m./sec.) (Fingers to Toes)	Confirmation of Diagnosis			Type of Coarctation and Remarks	
	Right Arm	Left Arm	Right Leg	Left Leg	Systolic	Diastolic	Hand	Toes	Ear Lobe	Scrotum	Left Hand	Right Hand		Angiocardiography†	Aortic Arteriography‡	Operation		
I	136/62 143/69	134/50	98/84? 90/57	112/94	— 53	— 3	11	5	2				4 5		+		Adult	
II	184/115 193/116	190/118	149/113 162/107		— 31	— 9	3	5	2				14 5		+		Adult, arterial hypertension	
III	180/110-0 214/57	110/70 124/70	Not obtainable 87/54		— 127	— 3	32	3	5		31	35	3 8	+	+	+	Adult, rheumatic heart disease	
IV	174/90 185/95	164/88	Not obtainable 118/90		— 67	— 5	9	1	14	1	9	10	Not obtainable		+		Adult, right undescended testis removed at the age of seventeen	
V	160/85	160/82	130/90	130/95													Adult, ? interventricular septal defect	
VI	164/78 184/92 200/80	182/90	107/75 140/115 110/70	130/110	— 57	— 3			25	5			4 9				Adult	
VII	118/70 125/70	100/?	Not obtainable 70/65		— 55	— 5	6	2	5	24	3	5	8	3 3	+		+	Infantile, not resectable
VIII	90/70 95/62	110/80	120/84? 90/63	124/80?	— 5	+ 1	7	5	3	7	5	12	8	3 7	+	+		Adult
IX	170/112 113/75†	172/104	Not obtainable 132/78†		+ 19†	+ 3†							10†			+	Adult, lumen 2 mm. in diameter	
X	118/78 135/70	102/76	152/118 125/70	148/102	— 10	0	16	4			6	4†		+			Not determined	
XI	188/90 205/92	190/94-60	Not obtainable 75/50		— 130	— 42	9	0	36	4	10	18	Not obtainable		+	+	Adult, lumen 1 mm in diameter	
XII	240/116	230/110	Not obtainable 94/86															
XIII	195/115§ 180/95 170/90	178/98	131/107§ Not obtainable 105/75		— 61	— 8	17	0	31	3	9	10	Not obtainable		0	+	Stenosis above renal arteries by calcified thrombus	
XIV	184/98 173/83	190/100	Not obtainable 95/70		— 65	— 15	4	1	20	2	4	4	5 4	+	+		Adult, not resectable	
					— 78	— 13	6	0	5	18	3	6	6	3 0	+	+	Adult, lumen 2 mm.	

* Upper readings by auscultatory method Lower readings (in italics) by direct arterial puncture.

† Eleven months postoperative.

‡ Performed by Drs. Thomas H. Burford and Merl J. Carson of Depts. of Surgery and Pediatrics.

§ Patient under general anesthesia

|| Performed by Dr. Thomas H. Burford

arteriography done a few days previously which required incision and repair of the left carotid artery.

These findings were confirmed at operation. A lumen of 1 mm. was found at the site of constriction. Six days later the patient was restudied. The double systolic peak of the pulse contour had disappeared and pulsations were now visible in the scrotum and toes. There was still evidence

Results of the study of the nine other patients were similar. (Table II.) Diastolic pressures in the legs, with the exception of Case XI, were from 0 to 15 mm. Hg lower than those in the arms. In seven of the patients it was 5 mm. or less. Diastolic hypertension (90 mm. or more) was present in the legs in only three patients; one of them, with the very mild coarctation, undoubtedly suffered from generalized arte-

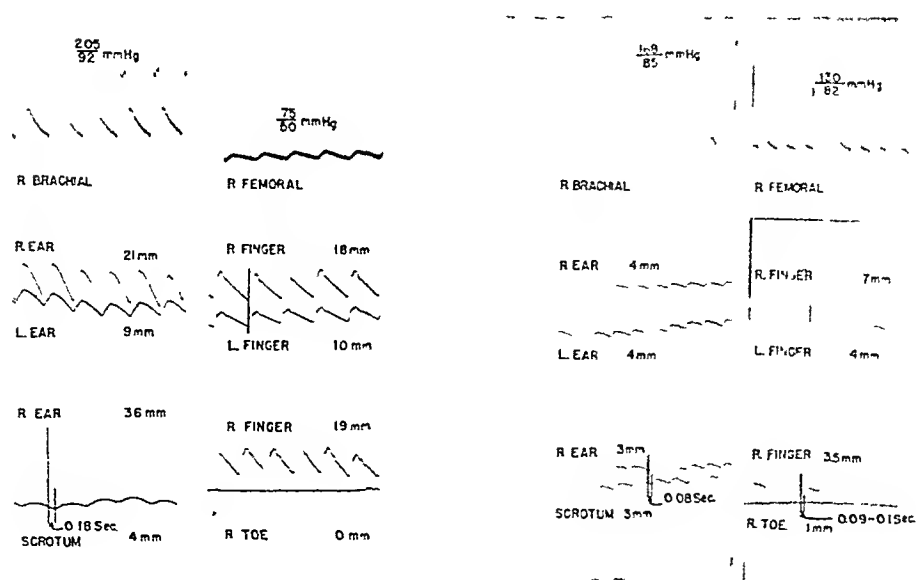


FIG. 4. Case XI, W. W. Photographic records of arterial pressure and photoelectric plethysmograms before (on the left) and after operation (on the right) for severe coarctation of the aorta. Note the very small pulsation in the femoral artery, toe and scrotum before operation. The difference in pulsations between the right ear and left may be due to involvement of the left carotid artery, which was opened three days previously for retrograde arteriography. After operation the changes are in the direction of normal. The pulse wave velocity between ear and scrotum is now within normal limits. There is, however, still a slight degree of coarctation as indicated by the differences of systolic pressure between the brachial and femoral arteries.

rial hypertension. (Case XI, Stewart and Bailey.)⁴ Another (Case XII) was found at autopsy to have obstruction of his aorta caused by a massive deposit of calcium just above the renal arteries. Elevation of the diastolic pressure was present in the arms but not in the legs in two other cases. The postoperative findings in one (Case IX) were normal.*

Use of the auscultatory method for obtaining blood pressure in the legs gave erroneously high readings of diastolic pressure in six cases; levels were unobtainable in eight.

The amplitude of the pulse wave in the ear lobe appeared to be larger in four patients with coarctation of the aorta than in normal subjects or in those suffering from arterial hypertension of other causes. That in the finger was higher in seven patients. While the series is admittedly small, these findings indicate a difference in degree of vascular activity in these areas in certain cases of coarctation.

* Eight additional cases have been studied, only one of which had diastolic hypertension in the legs.

COMMENTS

Only one Hamilton manometer was used to record the brachial and femoral arterial pressures. It is realized that simultaneous recordings would have been more desirable but the values obtained by subsequent measurements from one and then another extremity will give sufficiently accurate determinations for the differences found in coarctation of the aorta. The advantages of direct arterial puncture have been brought out in several instances. In severe coarctation the femoral pressure is often not obtainable by the auscultatory method. In the less severe cases a falsely high femoral pressure may be recorded. This was so in six of our patients. Only by direct arterial puncture can one obtain the true value and when this is done the milder cases of coarctation are readily established. Plethysmography offers confirmatory evidence.

The pathogenesis of the hypertension in coarctation of the aorta is controversial. That it is due to a general increase in arterial tone throughout the body has been

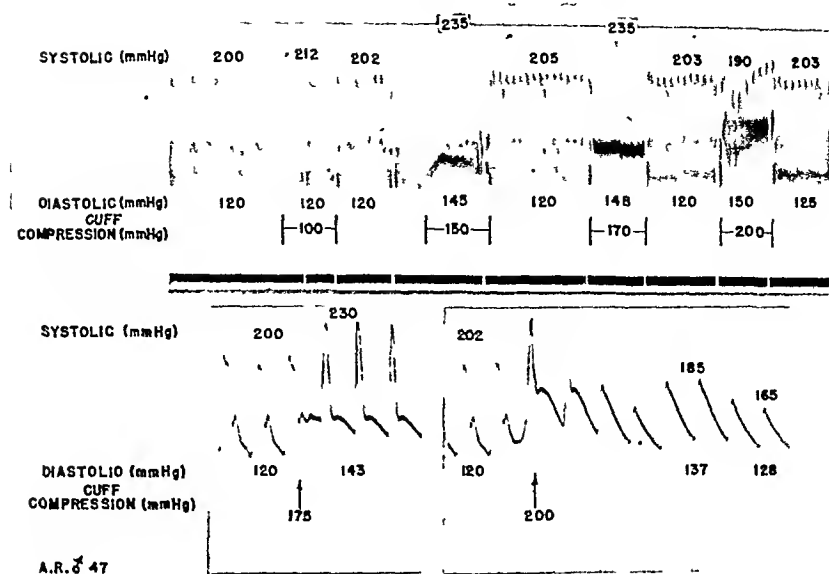


FIG. 5. A. R., the effect of partial occlusion of the brachial artery by a cuff upon blood pressure distal to the occlusion. In the upper curves the camera was moving at the rate of 1.25 mm. per second, the lower at 25 mm. per second. The figures at the top of the photograph refer to systolic pressure, those below to diastolic pressure and those between the vertical lines to compression of the cuff. Note the immediate rise of blood pressure when cuff compression is suddenly applied. Changes in the contour of the pulse wave are obvious (see text). At the high compressions the pulse wave appears similar to that seen in coarctation of the aorta. (Figs. 1, 2 and 4.)

advocated by Steele.^{5,6} That it is due to the mechanical effects of the lesion was suggested again by Hull⁷ and Bing.¹⁶ In the cases presented there is evidence that both mechanisms may be involved. Diastolic hypertension in the legs, which is usually accepted as evidence of generalized arteriolar constriction, was present in only two patients. One of them showed a lesion just above the renal arteries which was a counterpart of the experiment of Steele.⁸ It is a matter of interest that the diastolic pressure in the femoral artery was less than 60 mm. Hg in three patients, 60 to 80 mm. in seven patients and 80 to 90 mm. in none. The fact that the amplitude of the pulse wave in the upper part of the body was often higher (eight cases) than that seen in either uncomplicated hypertension or in normal subjects is further evidence for a mechanical factor being present. On the other hand, a low magnitude of the pulse similar to that seen in generalized hypertension was present in four cases, evidence for generalized vasoconstriction.

Hull⁷ has recently suggested an interesting experiment involving the use of two cuffs on the arm. The upper cuff was inflated to a level just above diastolic pressure and the lower used to measure blood pressure. Under these conditions diastolic pressure was observed to rise slightly and the systolic to fall. Wilkins and Bradley measured the changes in brachial arterial and venous pressure distal to a cuff by Hamilton manometers.⁹ The resultant systolic and diastolic pressure distal to the cuff was variable depending upon the amount of compression and the blood flow in the remaining part of the extremity. At certain critical supra-diastolic levels of pressure in the cuff both systolic and diastolic pressure rose and blood flow increased. This experiment was repeated in six subjects, three of them with arterial hypertension, two with coarctation of the aorta and one with a normal blood pressure. When the cuff was inflated to various levels in increments of 25 mm. Hg, the results were similar except that the change was much greater in hypertensive

subjects. At levels of partial occlusion above diastolic pressure both systolic and diastolic levels were observed to rise significantly on the next beat after occlusion. (Fig. 5, Table III.) At higher pressures, of course, systolic fell and diastolic did not. The con-

could be explained by the "breaker phenomenon" as proposed by Bramwell.¹¹ When a sea wave passes from deep water toward a beach, its crest travels faster than its trough, and the wave eventually breaks. The "beach" in this case is represented by

TABLE III
EFFECT OF PARTIAL ARTERIAL OCCLUSION UPON BLOOD PRESSURE DISTAL TO POINT OF OCCLUSION
(BRACHIAL ARTERY)

Control Blood Pressure (mm. Hg)	Cuff Compression			Control Blood Pres- sure (mm. Hg)	Cuff Compression		
	(mm. Hg)	(blood pres- sure mm. Hg)	(change)		(mm. Hg)	(blood pres- sure mm. Hg)	(change)
A. K. ♂ 45 Arterial Hypertension				A. R. ♂ 47 Arterial Hypertension			
250/132	50	247/132	— 3/0	200/120	100	212/120	+12/0
260/132	75	260/132	0/0	202/120	150	235/145	+33/+25
245/130	100	245/130	0/0	205/120	170	235/148	+30/+28
233/127	125	255/130	+22/+3	203/120	200	190/150	—13/+30
247/130	150	270/143	+23/+13	203/125	250	33*	
240/125	175	270/152	+30/+27				
248/127	200	275/145	+27/+18				
250/128	225	218/136	— 32/+8				
235/132	250	50*					
M. C. ♀ 43 Arterial Hypertension (mild)				D. W. ♂ 17 Normal			
150/80	50	150/80	0/0	120/60	50	117/55	— 3/—5
150/82	75	157/82	+ 7/0	119/60	75	120/60	+ 1/0
155/85	100	160/85	+ 5/0	115/55	100	120/70	+ 5/+15
150/85	125	165/95	+15/+10	110/55	120	90/65	—20/+10
160/90	150	145/100	—15/+10	115/60	150	5*	
160/90	175	30*					
H. W. ♂ 31 Coarctation of the Aorta				W. R. ♂ 26 Coarctation of Aorta			
170/92	90	170/90	0/—2	160/85	50	165/85	+ 5/0
162/90	100	170/95	+ 8/+5	160/87	75	165/85	+ 5/—2
167/93	118	175/95	+ 8/+2	159/84	95	170/85	+11/+1
163/87	130	185/110	+ 22/+23	160/85	125	173/100	+13/+15
165/90	150	165/115	0/+25	163/85	150	130/80	—33'—5
160/93	175	53/45	—107/—48	160/85	200	27*	
170/90	200	15*					

* Asystolic intra-arterial pressure thirty seconds after complete occlusion.¹⁵

Blood pressures are the average systolic and diastolic values for several beats. Although cuff compression appears to be greater than systolic pressure in patients D. W. and H. W., individual beats were at higher levels owing to natural variations.

tours of the pulses then approached those seen in coarctation.

The rate of rise of the pulse also increased when the cuff was inflated above diastolic pressure, a finding first described by Erlanger.¹⁰ This suggested that our results

the flattened artery under the cuff, which may so alter the wave front that it becomes steeper, and systolic pressure rises. Under these conditions diastolic pressure also rises, possibly because a turbulent flow has replaced one more or less smooth and the

coefficient of elasticity of the arterial wall under the cuff has been altered. Regurgitant flow is also abolished as suggested by Wilkins and Bradley. When the constriction is more severe, the form of the wave front alters further, becoming less steep, systolic pressure falling and diastolic pressure rising slightly. When the cuff is inflated to a level close to systolic pressure, both may become lower.

Attempts to reproduce this phenomenon in the femoral and renal arteries of dogs by means of a narrow clamp met with failure, probably because the distance over which the wave was altered was too small and the rigid clamp was not comparable to the elastic cuff. However, the narrow constriction of coarctation may so alter the aortic wave front as to cause some of the changes found in the femoral artery. All of these alterations were reproduced in the brachial artery by the experiment described.

Further, although controversial, evidence for the hypertension of coarctation of the aorta being different from the usual variety is offered by the insensitivity of these individuals to deoxycorticosterone acetate.¹² When this material is injected intravenously into patients with generalized arterial hypertension, a slow, sustained pressor response occurs. When it was given to six patients with coarctation of the aorta, no pressor response was elicited. One of them exhibited a high diastolic pressure and stenosis of the aorta above the renal artery.

It is possible to have a constriction of the aorta so severe as to prevent effectively the diastolic pressure in the leg from approximating that in the arm. (Case xi.) It is also possible to have a very mild coarctation. (Case ii.) All gradations between these two extremes may be found. A decision as to the advisability of surgical repair of the defect depends in part upon the degree of coarctation and in part upon the extent of collateral circulation. It is obvious that a clamp applied to the thoracic aorta would alter hemodynamics severely and might be extremely hazardous to the patient if a large proportion of the blood were going

through the constriction. Ordinarily we do not recommend surgery unless there is a marked difference (60 mm. Hg or more) in the systolic pressure of the brachial and femoral arteries as determined by direct puncture.

This method of study, while not new,¹³ has been of considerable aid in evaluating the hemodynamics of the circulation in coarctation of the aorta. Because the condition sometimes can be corrected by surgery, the use of these methods is of more than academic interest.

SUMMARY AND CONCLUSIONS

1. Fourteen cases of patients with coarctation of the aorta were studied by photoelectric plethysmography of peripheral parts and by direct measurements of brachial and femoral arterial blood pressure.
2. The hemodynamics of the circulation can be estimated by these methods, not only as an aid in locating the coarctation but in choosing patients suitable for surgery.
3. There is evidence that mechanical factors as well as humeral ones may operate to elevate blood pressure.

Acknowledgments. We are indebted to Dr. Edward Massie for referring Cases v, vi, xi and xiv; to Dr. Merl J. Carson for Cases iii, vii, viii, and x and to Dr. Thomas H. Burford for Cases xii and xiii. The technical help of Dr. John A. Nuetzel and Mary J. Kinsella is appreciated.

REFERENCES

1. HAMILTON, W. F., WOODBURY, R. A. and HARPER, H. T., JR. Physiological relationships between intrathoracic, intraspinal, and arterial pressures. *J. A. M. A.*, 107: 853, 1936.
2. FULTON, J. F. *Howell's Textbook of Physiology*, Philadelphia 1946. W. B. Saunders Company.
3. GOLDMAN, M. L., SCHROEDER, H. A. and FUTCHER, P. H. Coarctation of the aorta associated with abnormal digits, ovarian insufficiency, and shortness of stature. *J. Clin. Endocrinol.*, 9: 622, 1949.
4. STEWART, H. J. and BAILEY, R. L., JR. The cardiac output and other measurements of the circulation in coarctation of the aorta. *J. Clin. Investigation*, 20: 145, 1941.
5. STEELE, J. M. and COHN, A. E. The nature of hypertension in coarctation of the aorta. *J. Clin. Investigation*, 17: 514, 1938.

6. STEELE, J. M. Evidence for general distribution of peripheral resistance in coarctation of the aorta. *J. Clin. Investigation*, 20: 473, 1941.
7. HULL, E. On the evidence for generalized arteriolar constriction in coarctation of the aorta. *Am. Heart J.*, 35: 980, 1948.
8. STEELE, J. M. Effect of partial clamping of the aorta in dogs upon diastolic pressure in carotid and femoral arteries. *Proc. Soc. Exper. Biol. & Med.*, 41: 86, 1939.
9. WILKINS, R. W. and BRADLEY, S. E. Changes in arterial and venous blood pressure and flow distal to a cuff inflated on the human arm. *Am. J. Physiol.*, 147: 260, 1946.
10. ERLANGER, J. Studies in blood pressure estimation by indirect methods. *Am. J. Physiol.*, 40: 82, 1916.
11. BRAMWELL, J. C. The change in form of the pulse wave in the course of transmission. *Heart*, 12: 23, 1925.
12. GOLDMAN, M. L. and SCHROEDER, H. A. The immediate pressor effects of desoxycorticosterone acetate in arterial hypertension. *Am. J. Med.*, 5: 33, 1948.
13. MEGIBOW, R. S. and FEITELBERG, S. Application of microplethysmography to the diagnosis of patent ductus arteriosus and coarctation of the aorta. *Am. J. Med.*, 4: 798, 1948.
14. HARTMANN, ALEXIS F. Conference at St. Louis Children's Hospital. *J. Pediat.*, 32: 26, 1948.
15. WILLIAMS, A. H. and SCHROEDER, H. A. The asystolic arterial pressure gradient as a measure of local peripheral resistance. *Am. J. Physiol.*, 155: 132, 1948.
16. BING, R. J., HANDELSMAN, J. C., CAMPBELL, J. A., GRISWOLD, H. E. and BLALOCK, A. The surgical treatment and the physiopathology of coarctation of the aorta. *Ann. Surg.*, 128: 803, 1948.

Acute Coronary Insufficiency Due to Pulmonary Embolism*

SIMON DACK, M.D., ARTHUR M. MASTER, M.D., HENRY HORN, M.D.,
ARTHUR GRISHMAN, M.D. and LEONARD E. FIELD, M.D.

New York, New York

THE interest aroused by the report of McGinn and White¹ on acute cor pulmonale led to many studies²⁻¹⁰ of the electrocardiographic changes and other cardiac sequelae of embolism of the pulmonary artery. The electrocardiographic pattern described by McGinn and White is distinguished by a deep S₁ and Q₃, depression of the RS-T segment in Lead I, elevation of this segment in Lead III and inversion of T₃ or of T₂ and T₃, and was believed by these authors to be caused by acute right ventricular strain secondary to obstruction of the pulmonary artery. Our experience, however, indicates, as does that of several other authors,^{4,8,11} that this pattern appears in a minority of patients with embolism of the pulmonary artery. In most of these patients the electrocardiographic changes consist chiefly of depression of the RS-T segment and inversion of the T wave in one or more leads, without a deep S₁ or Q₃. Since similar deviations follow acute coronary insufficiency precipitated by shock and hemorrhage,¹² it is apparent that such changes cannot be attributed solely to right ventricular strain.

Several factors may contribute to the cardiac and peripheral circulatory sequelae of embolization of the pulmonary artery. The purpose of this paper is to review briefly the physiologic aspects of the cardiovascular disturbances in pulmonary embolism and to evaluate the factors of right ventricular strain and failure, hyposystolic or forward

failure, generalized anoxia or asphyxia and myocardial anoxia due to coronary insufficiency in the light of the clinical, electrocardiographic and anatomic findings. As we shall see, the predominant exciting factor is acute coronary insufficiency rather than right ventricular strain. Acute coronary insufficiency may be responsible not only for the electrocardiographic abnormalities but also for the acute myocardial changes in the left ventricle, which are far more serious than the involvement of the right ventricle.

Acute coronary insufficiency is the term we use to designate disproportion between nutritional requirements of the myocardium and its supply of coronary blood, resulting in absolute or relative deficiency of the coronary circulation. The term should not be construed to include thrombotic occlusion of the coronary artery.

Previously^{12,13} we presented evidence that acute coronary insufficiency is a disease entity which is precipitated by several groups of factors. Severe exertion or emotional stress, tachycardia, hypertension, hyperthyroid crises, acute infections and drugs such as adrenalin and insulin, by elevating blood pressure, heart rate or cardiac output increase the work of the heart and thereby the myocardial requirement for blood, thus creating a relative coronary insufficiency. Shock, hemorrhage, hypotensive crises, acute heart failure, pulmonary embolism and coronary vaso-

* From the Cardiographic Department and the Medical Services, The Mount Sinai Hospital, New York. Presented before the Eastern Section of the American Federation for Clinical Research, December 14, 1946, New York, N. Y.

constriction may diminish the coronary blood flow by lowering the blood pressure and the cardiac output. The third group of factors consists of conditions which impair oxygenation of the blood or diminish its oxygen-carrying power; i.e., anesthesia, high altitude, carbon monoxide poisoning, acute anemia, pulmonary embolism, acute bronchial asthma and pulmonary insufficiency.

Acute coronary insufficiency is most likely to develop when predisposing factors which produce chronic deficiency of coronary blood flow with myocardial anoxia are present. These factors may be structural in nature, such as coronary arteriosclerosis, aortic valvular disease and cardiac hypertrophy; or non-structural, such as congestive heart failure and anemia.

When coronary insufficiency is sufficiently prolonged or severe, the ensuing myocardial ischemia and anoxia often cause acute degenerative or necrotic changes in the myocardium. These myocardial lesions vary in size from microscopic areas of necrosis to gross areas of infarction. They are characteristically focal, disseminated and situated in the subendocardial layer of the left ventricle particularly in the papillary muscles.

The electrocardiogram in acute coronary insufficiency is characterized by depression of the RS-T segment and inversion of the T wave in one or more leads, often in all leads, including the precordial. These deviations are due to the subendocardial localization of the myocardial ischemia. The electrocardiographic changes are reversible and may disappear with elimination of the precipitating factors and subsidence of the coronary insufficiency. Deep Q waves and elevation of the RS-T segment, typical of acute coronary occlusion, do not occur in acute coronary insufficiency.

HISTORICAL SURVEY

Virchow¹⁴ as early as 1856 attributed sudden death that occurred in a case of pulmonary embolism to "cardiac asphyxia and arrest" brought about by interference

with the coronary blood flow. To explain the severe clinical symptoms caused by formation of small emboli in the lungs, it was suggested many years ago that reflexes which are mediated through the vagus nerve and elicited in the wall of the obstructed and distended pulmonary arteries cause widespread reflex pulmonary arteriolar constriction¹⁵ and reflex stimulation of the respiratory center.¹⁶ The latter is probably responsible for the tachypnea characteristic of these cases. Experimentally^{7,16,17} this vagal reflex has been blocked by vagotomy or by administration of atropin and papaverine. It has also been demonstrated¹⁸⁻²⁰ that mechanical obstruction or ligation of the pulmonary artery for from 60 to 70 per cent of its cross-section area may not interfere significantly with the pulmonary circulation or produce pulmonary hypertension. On the other hand, distinct circulatory and cardiac effects are often noted following embolism even when the main pulmonary artery is uninvolved.²¹ It is possible, therefore, that reflex constriction of the pulmonary arterioles may be an important factor in production of pulmonary hypertension in clinical pulmonary embolism. That vagal stimulation of considerable degree occurs in pulmonary embolism is evidenced by the not infrequent disturbances in sino-auricular and auriculo-ventricular conduction with resulting sinus arrest, sino-auricular block, nodal rhythm and auriculo-ventricular dissociation.⁷

Since 1933 a number of European workers^{2,22-24} have alluded to the occurrence of a pulmonocoronary reflex mediated through the vagus nerve, which has been considered responsible for reflex vasoconstriction of the coronary arteries. Scherf and Schoenbrunner,² among the earliest proponents of this theory, ascribed precordial pain and other cardiac disturbances in pulmonary embolism to such reflex coronary vasoconstriction. However, more recent work^{21,25} casts doubt upon the validity of this explanation. It has been found that bilateral cervical vagotomy does not abolish the electrocardiographic changes

that appear following experimental pulmonary embolism. Furthermore, studies with Rein's flowmeter in experimental embolization²⁶ of the pulmonary artery show an increase in the minute volume flow in the right coronary artery, an observation that nullifies the theory of the existence of reflex constriction. Even in the presence of an increased coronary flow, coronary insufficiency and myocardial anoxia may be provoked if the increased flow is insufficient to compensate for the additional requirements of the ventricles and the increased work of the right side of the heart.

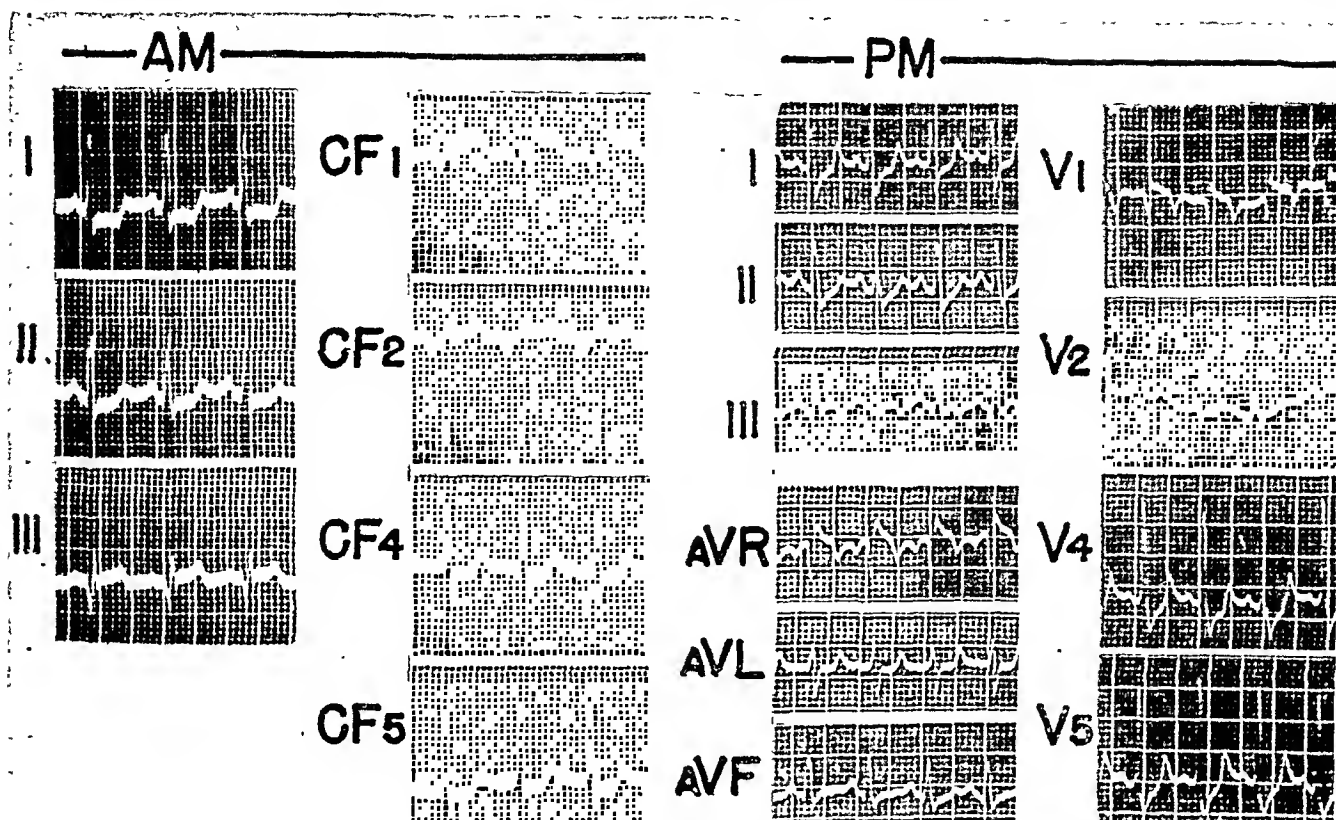
Nevertheless, changes of such degree occur in the hemodynamics of the pulmonary and systemic circulations that it is unnecessary to invoke the mechanism of reflex coronary constriction.²¹ Eckardt²⁶ demonstrated that embolism of the pulmonary artery and increased pressure in the pulmonary artery are followed by diminution in arterial pressure, transitory decrease in coronary blood flow and then sustained increased flow particularly in the right coronary artery. He ascribed the drop in systemic blood pressure to the mechanical and reflex obstruction of the pulmonary blood flow, decreased return to the left ventricle and diminished cardiac output. This mechanism constitutes an important basis for forward failure of the left ventricle and coronary insufficiency in pulmonary embolism.²⁷ In 1937 Daly and his co-workers²⁸ and Schweigk²⁹ independently discovered a reflex relationship between the pulmonary and the systemic circulations. They showed that in animals with independent circulation in the pulmonary and systemic circuits, elevation of pulmonary artery pressure lowered systemic arterial pressure, independent of variations in venous return or cardiac output. In dogs this reflex effect was abolished by section of the cervical vagosympathetic nerves. Subsequent investigators^{7,30} confirmed the existence of this reflex depressor mechanism and showed that it was the basis for the fall in systemic blood pressure and shock which occur in clinical pul-

monary embolism. In their recent review of cardiodynamics of experimental pulmonary embolism Megibow, Katz and Steinitz²¹ state that increased pressure in the pulmonary artery and the right ventricle leads to increased work of the right side of the heart, diminished coronary blood flow, coronary insufficiency and gradual or rapid heart failure.

There are numerous reports^{5,7,27,31-33} of electrocardiographic changes observed following experimental pulmonary embolism and compression of the pulmonary artery. Although the deviations noted were not uniform, a large percentage of the electrocardiograms showed changes in the RS-T interval and T wave which could be attributed to coronary insufficiency and myocardial anoxemia.

Anatomic studies in both experimental and clinical pulmonary embolism afford corroborative evidence of the role played by coronary insufficiency and myocardial anoxia in this condition. Following experimental production of pulmonary embolism, Buchner and his associates³⁴ found focal areas of myomalacia in the right ventricle which they believed were due to coronary insufficiency. They reasoned that right ventricular dilatation and failure diminished blood flow in the right coronary artery; this resulted in ischemia, anoxia and necrosis of the right ventricular myocardium.

More recently Horn, Dack and Friedberg⁶ observed acute myocardial changes in approximately 20 per cent of forty-two fatal cases of pulmonary embolism. In none of these cases was there a history of recent coronary occlusion. In an earlier study of myocardial infarction without acute coronary occlusion Friedberg and Horn³⁵ found that approximately one-fourth of the cases of infarction occurred in patients dying of recurrent embolism of the pulmonary artery. The myomalacia observed in the two studies was generally focal and subendocardial, localized in the left ventricle and was attributed to the effect of shock and anoxemia on the coronary circulation. In two of these cases focal myocardial necrosis was found



1A

FIG. 1A. E. V., a female, age forty years, experienced epigastric pain fifteen days after bilateral salpingo-oophorectomy. Seven hours later peripheral collapse developed and she died two hours thereafter. Autopsy revealed bilateral pulmonary embolism of the right main and left lower lobe branches. The coronary arteries were normal. The heart was grossly normal except for mottling of the posterior papillary muscle of the left ventricle. Microscopic examination in this area revealed focal myonecrosis (Fig. 1B.). Electrocardiogram taken soon after the onset of symptoms in the morning (A.M.) showed a small S_1 and deep Q_3 , depression of RS-T in Leads I, II, CF_4 and CF_5 and elevation in Leads III and CF_1 . At this time differentiation could not be made between acute cor pulmonale and acute posterior wall infarction due to coronary occlusion. The record taken several hours later in the afternoon (P.M.), however, showed the pattern of acute cor pulmonale, characterized by prominent S waves in Leads I, II, V_4 and V_5 , small Q_3 , prominent R and elevated RS-T in Leads AVR and V_1 and depressed RS-T in Leads I, II, V_4 and V_5 and an inverted T_3 . It is of interest that myocardial ischemic changes secondary to acute coronary insufficiency developed in the presence of the classical cor pulmonale pattern in the electrocardiogram.

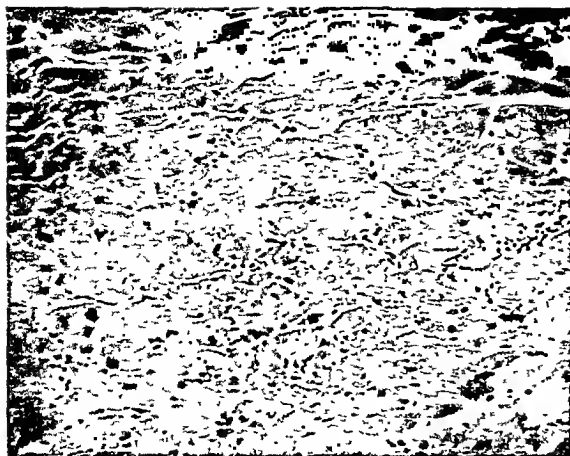
also in the right ventricle. Isolated right ventricular necrosis was not observed. From these observations it may be concluded (1) that coronary insufficiency following pulmonary embolism is generalized, affecting the left coronary artery as well as the right and (2) that the left ventricle is more susceptible than the right to the effect of coronary insufficiency.

Subsequently Currens and Barnes^{9,10} found four cases of recent myocardial infarction without acute coronary occlusion among thirty fatal cases of pulmonary embolism. In three of the four instances infarction involved both ventricles. These authors also attributed the infarction to coronary insufficiency resulting from shock

and increased pressure within the right side of the heart.

MATERIAL

The present report is based on clinical and pathologic study of forty-one consecutive fatal cases of pulmonary embolism. In all cases one or more electrocardiograms were obtained following occurrence of the pulmonary embolism. The clinical status of the patients and the electrocardiograms obtained during the acute attacks were reviewed and correlated with the anatomic findings. Eighteen of the patients were men and twenty-three were women. Twenty-two were non-surgical cases; nineteen occurred postoperatively.



1B

FIG. 1B. Section of posterior papillary muscle of left ventricle showing loss of striation, lysis of fibrils, early necrosis and reactive polymorphonuclear leukocyte infiltration. These represent early ischemic myocardial alterations incident to acute coronary insufficiency which resulted from shock and diminished coronary blood flow. Although the insufficiency was of relatively short duration, it was sufficiently severe to have produced focal myonecrosis even in the presence of normal coronary arteries.

RESULTS

Electrocardiographic Findings. The electrocardiograms were classified in four groups: Group I comprised fifteen cases presenting the general pattern of acute cor pulmonale; Group II, seventeen cases which presented the electrocardiographic deviations associated with coronary insufficiency, i.e., RS-T depressions and T wave inversions; Group III, six cases with atypical electrocardiographic changes which did not fall into either one of the first two groups; Group IV, three cases in which the electrocardiograms showed little or no variation from the tracings made before embolization occurred.

Group I—Cor Pulmonale Pattern. Eight patients presented the electrocardiographic pattern of acute cor pulmonale, that is, deep S_1 and Q_3 , depressed RS-T in Lead I, elevated RS-T in Lead III and inverted T_3 . (Fig. 1A.) In three other patients the pattern was similar except for the absence of a deep S_1 . The remaining three patients presented deep S_1 and Q_3 but changes in the RS-T segment or T wave were absent. The T wave was inverted in Lead II in one

case and in another it was inverted in CF_4 . Atypical right bundle branch block was observed in three of the fifteen patients.*

Group II—Coronary Insufficiency Pattern. Electrocardiograms of this group disclosed depression of the RS-T segment and inversion of the T wave in one or more leads. (Fig. 2.) In ten cases the deviations occurred in all four or in three of the four leads; it was more common in Lead I than in Lead III. In five cases the RS-T segment was slightly elevated in Lead III. Depression of the RS-T segment occurred without T wave inversions in eight cases, but inverted T waves unaccompanied by RS-T deviations were infrequent occurring only twice. In three cases a small S_1 or S_1 and Q_3 were suggestive of acute cor pulmonale.

Group III—Atypical Electrocardiographic Changes. Six patients presented atypical acute electrocardiographic changes. In four of these intraventricular or bundle branch block was present prior to the pulmonary embolism and miscellaneous abnormalities involving the RS-T segment or T wave appeared subsequently. The RS-T segment was elevated in all leads in one case, in Leads I and II in another case and in Lead III in a third case. These atypical electrocardiographic changes were obviously related to the conditions underlying the abnormal records which antedated the embolic incidents.

Group IV—No Acute Electrocardiographic Changes. In the three cases in this group the electrocardiograms made following embolism of the pulmonary artery did not differ materially from the previous abnormal records which were the result of long-standing heart disease.

Associated Electrocardiographic Changes. Intraventricular conduction disturbances may appear following embolism of the pulmo-

* In one case in which multiple precordial and unipolar leads were recorded the RS-T segment was depressed over the left side of the precordium (V_4 to V_6) and elevated over the right side of the precordium (V_1) and in the unipolar lead from the right arm (VR). We have observed a similar pattern in acute coronary occlusion with posterior wall infarction and in acute coronary insufficiency from any cause.

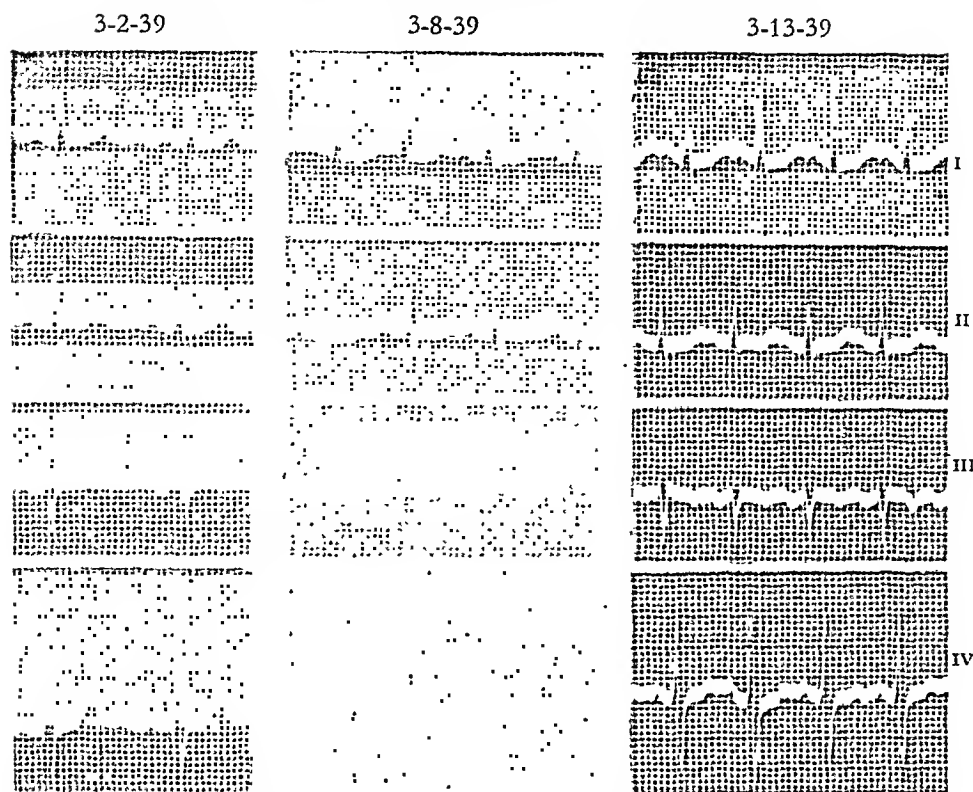


FIG. 2. J. K., a seventy-one year old man developed acute pulmonary artery embolism on March 8th, four days after resection of a carcinoma of the rectum. The patient died on March 14th. Autopsy revealed an embolic occlusion of the left main pulmonary artery. The coronary arteries were patent. The myocardium showed focal fibrosis and there were no acute changes either on gross or microscopic examination. The electrocardiogram taken prior to the embolic episode was normal except for left axis deviation. On March 8th, several hours after the onset of embolism, the S-T segment became depressed and the T wave semi-inverted in Leads I, II and CF₄. The record on March 13th was practically the same. These changes are those of acute coronary insufficiency.

nary artery,³⁶ usually within the first twenty-four to thirty-six hours. The intra-ventricular block is generally of the atypical right bundle branch block type; it may be transient. Atypical right bundle branch block developed in three of the cases in Group I (cor pulmonale) and persisted until death intervened early in the attack. In two other cases a left and a right bundle branch block pattern antedated the embolism.

Well defined right axis deviation was present in only five cases, three in Group I and two in Group II. Left axis deviation, on the other hand, appeared in eleven cases. In the majority of the latter the axis deviation preceded the embolic episode and was believed to have resulted from previous hypertensive and arteriosclerotic heart disease. (Figs. 4A and 5.)

Cardiac arrhythmias were observed in

seven cases. Auricular tachycardia occurred twice, auricular fibrillation once and heart block once. In the latter case there was associated sino-auricular block and ventricular fibrillation occurred terminally. Similar arrhythmias have been observed in pulmonary embolism experimentally produced.^{7,33,37}

The influence of various predisposing and precipitating factors in Groups I and II was evaluated. These included age, sex, antecedent cardiac disease, right ventricular strain and other anatomic changes observed during postmortem examination.

Age and Sex Incidence. There was a slightly higher incidence of women than men in the series and also in the individual groups, but the sex of the patients and the electrocardiographic pattern following pulmonary embolism were not apparently associated. On the other hand, the age of

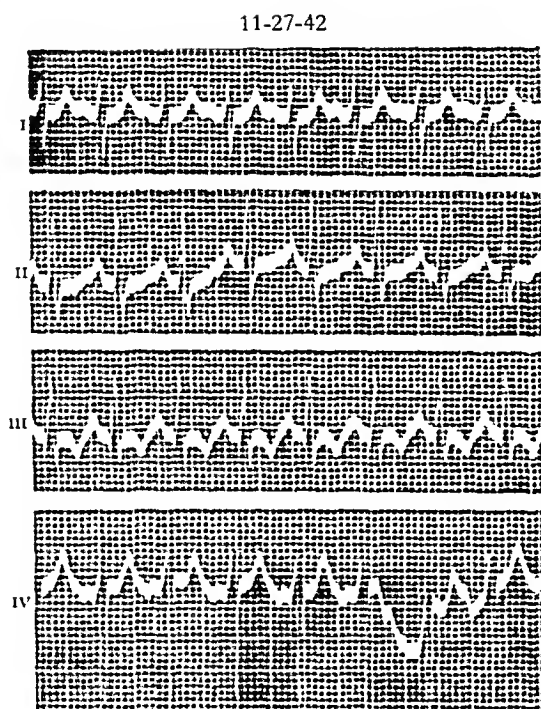


FIG. 3. E. P. was an eighteen year old boy with recurrent pulmonary embolism of two weeks' duration. A massive embolism occurred several hours prior to admission and ended fatally during an attempted pulmonary artery embolectomy. Autopsy revealed emboli to variously sized pulmonary artery branches with associated multiple pulmonary infarcts. The origin of the emboli was undetermined. The electrocardiogram showed the cor pulmonale pattern characterized by right axis deviation, deep S_1 and S_2 , semi-inverted T_2 and inverted T_3 . It differs from the classical pattern in the absence of a prominent Q_1 .

the patient seemed to influence the electrocardiographic pattern. Of thirteen patients below the age of fifty, seven fell into Group I (cor pulmonale) and only two into Group II (coronary insufficiency). Of twenty-eight patients aged fifty years or more only eight fell into Group I while fifteen were in Group II. The coronary insufficiency pattern occurred more often in the older individuals in whom arteriosclerotic or hypertensive heart disease co-existed.

Antecedent Cardiac Disease. The foregoing observation was borne out by analysis of the cardiac status of the patients prior to occurrence of pulmonary embolism. One-half of the patients with acute cor pulmonale pattern (Group I) had clinical evidence of hypertension or coronary artery disease;

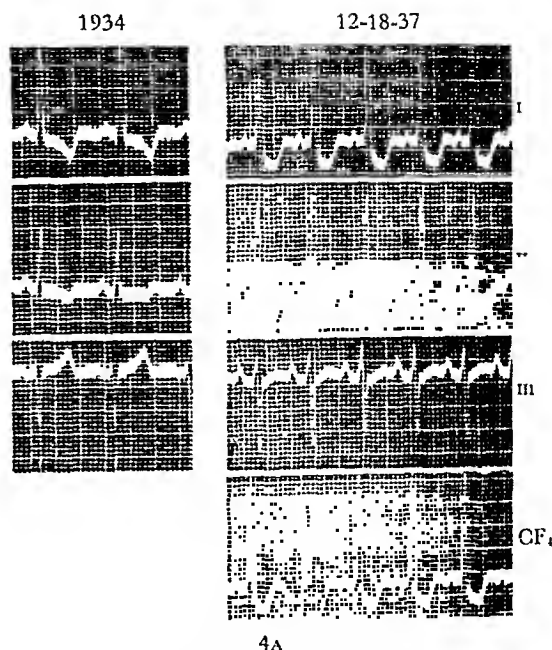


FIG. 4A. A. F., a female aged fifty-four years, suffered with antecedent hypertensive heart disease of ten years' duration. Three weeks after a mild cerebrovascular accident she developed increasing dyspnea, restlessness, impaired heart sounds, drop in blood pressure and partial heart block. This was followed by tachycardia, tachypnea, labored breathing and death three days later. Autopsy showed multiple acute and organizing pulmonary artery emboli and pulmonary infarcts. The heart was hypertrophied, weighing 430 Gm.; the coronary arteries were normal. Focal subendocardial necrosis was noted involving the interventricular septum, anterior wall of the left ventricle and papillary muscles of both ventricles. The electrocardiogram taken in 1934 showed the typical "hypertensive" pattern of left ventricular enlargement, i.e., left axis deviation, high voltage QRS, RS-T depressed in Lead I and elevated in Lead III, T_1 deeply inverted and T_2 diphasic. On December 19, 1937, one day prior to death, there was striking RS-T depression in Leads I, II and CF_4 , and slight depression in Lead III. These changes are characteristic of acute coronary insufficiency, the cause for the subendocardial myocardial necrosis. (Figs. 4B and C.)

three-fourths of the patients with coronary insufficiency (Group II) and all the patients with atypical electrocardiograms (Group III) had hypertension or arteriosclerosis. The classical picture of cor pulmonale appeared most often in the patients with previously normal hearts, whereas the antecedent cardiac disease seemed to be the predisposing factor in the development of coronary insufficiency. (Figs. 4 and 5.) When the electrocardiogram made prior to pulmonary

ECG in Pulmonary Embolism—*Dack et al.*

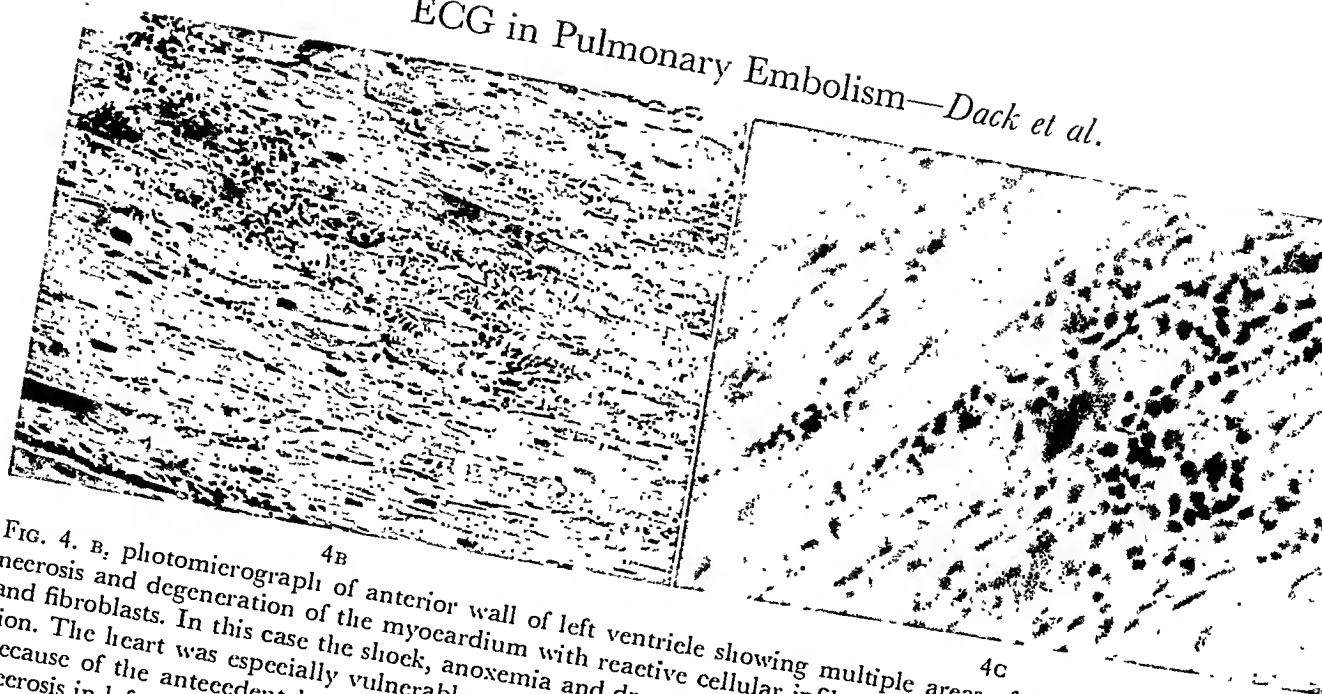


FIG. 4. B, photomicrograph of anterior wall of left ventricle showing multiple areas of focal acute and subacute necrosis and degeneration of the myocardium with reactive cellular infiltration by polymorphonuclear leukocytes and fibroblasts. In this case the shock, anoxemia and drop in blood pressure led to a decrease in coronary circulation. The heart was especially vulnerable to deficiency of coronary blood flow and associated myocardial anoxia because of the antecedent hypertension and cardiac hypertrophy. C, higher magnification of area of focal myocardial necrosis in left ventricle.

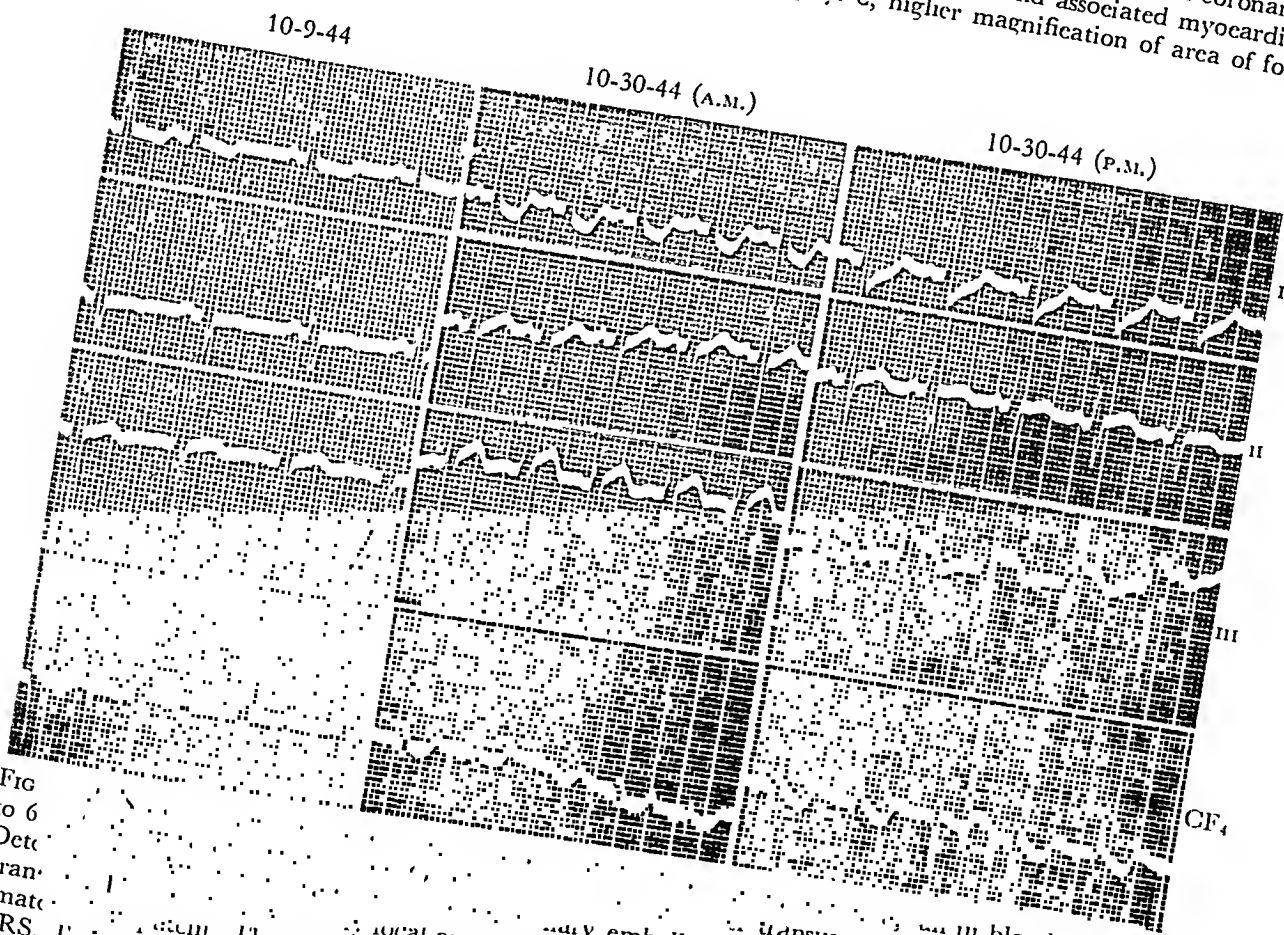


FIG. 5. ECG tracings showing changes in blood pressure and local areas of fatty degeneration. The coronary arteries were atherosclerotic. The preoperative electrocardiogram showed left axis deviation, high voltage QRS, T_1 inverted, T_2 and T_4 semi-inverted. This record suggests left ventricular enlargement and myocardial involvement. On October 30th, one day after the embolic episode, there were more striking RS-T depressions in Leads I and CF_4 and elevation in Lead III which persisted until death. These changes are indicative of acute coronary insufficiency. It is of interest that in the presence of a "left ventricular strain" pattern the acute coronary insufficiency intensified the S-T depression in Lead I and the elevation in Lead III.

embolism was very abnormal, the electrocardiographic changes following embolism were usually those of coronary insufficiency or, in a few instances, atypical. Furthermore, existing marked left axis deviation made development of the cor pulmonale pattern less likely. When left axis deviation was associated with RS-T deviations (depression in Lead I, elevation in Lead III), the latter were infrequently intensified by the coronary insufficiency. (Fig. 5.)

Cardiac Enlargement. Correlation of the electrocardiographic pattern with the actual weight of the heart corroborated the clinical observations. Distinct cardiac enlargement (heart weight 400 Gm. or over) was found in 14 per cent of the patients with cor pulmonale electrocardiograms and in 59 per cent of those with coronary insufficiency records, a finding that indicates the importance of cardiac hypertrophy as a predisposing factor in the development of coronary insufficiency following pulmonary embolism.

Right Ventricular Strain. Incidence and degree of dilatation of the right side of the heart was observed at necropsy in the thirty-two patients comprising Groups I and II. Dilatation of the right ventricle was found in seven of the fifteen cases of cor pulmonale and in eight of the seventeen cases of acute coronary insufficiency. Right ventricular dilatation was not, therefore, regularly associated with either a "cor pulmonale" or a "coronary insufficiency" electrocardiogram. As a matter of fact, the pattern of coronary insufficiency appeared most often in patients with marked dilatation of the chambers of the right side of the heart, a finding which suggests that coronary insufficiency and right ventricular strain may occur simultaneously following massive embolism of the pulmonary artery. That coronary insufficiency may be the dominant factor in the clinicopathologic abnormalities, however, is indicated by the myocardial damage found in such cases.

Pathologic Myocardial Changes. A detailed anatomic study of the heart was made in all cases. Many blocks of the ventricular

walls including the papillary muscles were taken for microscopic study and the coronary arteries were sectioned at close intervals. Evidence of myocardial necrosis was found in ten of the cases (24 per cent): in three cases gross changes were present in the myocardium and in seven cases, histologic changes. Acute occlusion of a coronary artery was not seen in any of the hearts.

The gross myocardial changes consisted of focal, disseminated areas of yellowish-red mottling in the subendocardial layer of the myocardium involving especially the papillary muscles of the left ventricle. In one case the anterior wall of the left ventricle was involved, and in two cases both surfaces of the left ventricle were affected. In one of the latter cases there was also focal infarction of the right ventricle. Microscopic examination of the lesions revealed degenerative alteration of the muscle fibers, focal hemorrhage and necrosis. The latter had provoked reactive cellular infiltrates of polymorphonuclear leukocytes, histiocytes and fibroblasts. These lesions differed in no way from those observed in cases of acute coronary insufficiency precipitated by other factors, such as shock, drop in blood pressure and hemorrhage.¹²

Five of the cases of focal myocardial necrosis were in Group I, four in Group II and one in Group IV. In other words, acute myocardial changes were found among the patients with clinical signs of cor pulmonale as frequently as among those with clinical evidence of acute coronary insufficiency. The myocardial changes in the four cases of coronary insufficiency (Group II) were, however, decidedly more severe than the changes in the cases of cor pulmonale (Group I). In three of the four hearts of Group II gross infarction was fairly extensive (Figs. 4B and 4C); in the five hearts of Group I infarction was detected only on histologic examination.

The ten cases of focal myocardial infarction were analyzed with a view to determining the nature of the factors which had predisposed the patients to acute coronary

insufficiency. In eight cases evidence of antecedent arteriosclerotic or hypertensive heart disease was found. There was moderate to severe stenosis of the coronary arteries in four of the hearts. When the coronary arteries were patent, the hearts were distinctly hypertrophied and enlarged. Four patients had sustained multiple pulmonary lesions and had lived from two to three weeks following initial embolization. One patient with a heart normal in size and patent coronary arteries lived only nine hours. The embolism, however, involved all the branches of the pulmonary artery as well as the main stem, and the profound degree of shock and anoxemia produced intense coronary insufficiency despite absence of predisposing arteriosclerotic factors.

In summary, it may be said that coronary insufficiency and focal myocardial infarction had a tendency to follow pulmonary embolism in those cases in which there was pre-existing coronary arteriosclerosis or cardiac hypertrophy, particularly when the embolism was multiple and the duration of life following the onset was sufficiently long to permit development of anatomic myocardial changes.

COMMENT

Analysis of forty-one fatal cases of embolism of the pulmonary artery indicates that acute coronary insufficiency is an important factor in determining the electrocardiographic picture and the myocardial effects that follow embolism. So much attention has been directed toward the right ventricular dilatation and strain following pulmonary embolism that sight has been lost of the fact that the left ventricle is affected deleteriously and often to a greater extent than the right ventricle. In our series the electrocardiographic pattern of acute coronary insufficiency occurred more often than did the pattern of *cor pulmonale*, and myocardial necrosis involved the left rather than the right ventricle.

The electrocardiographic and anatomic changes attributable to acute coronary

insufficiency were found for the most part in the older individuals and in those with clinical or anatomic evidence of antecedent heart disease. In other words, acute coronary insufficiency is more likely to follow pulmonary embolism in patients with chronic coronary insufficiency than in those individuals who have previously been free of cardiac abnormalities. On the other hand, the classical *cor pulmonale* pattern and right ventricular strain occurred most often in those patients whose hearts were previously normal.

The mechanism underlying development of coronary insufficiency following embolism of the pulmonary artery can be explained by the known physiopathologic effects produced by obstruction of the pulmonary artery. Our observations offer clinico-pathologic evidence that the important exciting factors of the diminished coronary blood flow and myocardial anoxia are systemic shock, right ventricular dilatation, anoxemia and possibly reflex coronary vasoconstriction.

Shock. Shock was an almost universal feature in our series of cases. It occurred in patients with *cor pulmonale* as often as in those with coronary insufficiency; it was most severe in those patients in whom ischemic or anoxic changes of the myocardium developed. It has been stated^{6,7,21,26,27,29} that obstruction of the pulmonary artery, as well as clinical pulmonary embolism, leads to lowering of systemic blood pressure, diminished venous return to the left ventricle, diminished left ventricular stroke output and shock. These circulatory disturbances eventually result in diminished coronary blood flow and nutritional disturbances in the myocardium of both ventricles but more particularly the left. When the shock is intense and prolonged and the coronary circulation has been impaired previously by coronary arteriosclerosis or cardiac hypertrophy, the myocardial anoxia may progress to focal degeneration or subendocardial necrosis in the myocardium. The site of the necrosis is usually the left ventricle.

Right Ventricular Dilatation. Both clinical and postmortem observations have demonstrated that acute dilatation and strain of the right ventricle is a common sequel to massive embolism of the pulmonary artery. Accentuation of the pulmonic second heart sound, right ventricular failure and the typical $S_1 Q_3$ pattern in the electrocardiogram are the usual clinical signs of right ventricular dilatation and strain.³⁸ In our series distinct right ventricular dilatation, often of a marked degree, was found at autopsy in approximately one-half of the cases.

It is significant that autopsy revealed that right ventricular dilatation occurred as frequently in cases with electrocardiographic records of coronary insufficiency as in those with records of right ventricular strain. Conversely, in half of the cases in which isolated right ventricular dilatation was found at autopsy, the electrocardiograms showed changes characteristic of acute coronary insufficiency. Furthermore, right ventricular strain was found in approximately half of the cases of focal myocardial infarction of the left ventricle. These observations afford further evidence that acute coronary insufficiency may be the dominant factor underlying the electrocardiographic changes and myocardial involvement even when right ventricular strain exists. It has been suggested^{9,10} that right ventricular strain may contribute to the development of coronary insufficiency. This theory based on clinical grounds is in agreement with the observations of investigators^{21,39} who found that following experimental obstruction of the pulmonary artery the increased right ventricular pressure was associated with diminution in coronary blood flow, particularly in the right coronary artery. Megibow, Katz and Steinitz²¹ attributed the coronary insufficiency to extravascular compression of the Thebesian veins and interference with emptying of the coronary sinus and veins.

It might be assumed that in the presence of right ventricular strain, with resulting increase in nutritional requirements of the

right ventricle, the right ventricle would be the site of predilection for the morphologic sequelae of acute coronary insufficiency. This theory seems to be borne out by the work of Buchner and his associates³¹ who found that pulmonary embolism in animals induced right, rather than left, ventricular myomalacia. They attributed this result to diminution of flow in the right coronary artery. Currens and Barnes¹⁰ reported one patient with isolated infarction of the right ventricle. In our series, however, involvement of the right ventricle was in all cases associated with involvement of the left. The fact that the left ventricle was affected much more frequently and to a much greater degree than the right ventricle suggests that the left ventricle is more susceptible than the right to acute coronary insufficiency, even when right ventricular strain and dilatation are present. The increase in ventricular pressure that follows embolism may produce greater diminution of blood flow in the right coronary artery than in the left coronary artery, thereby affecting chiefly the posterior wall. We believe, however, that this resemblance may be incidental and that right ventricular dilatation and cardiac rotation are important causes for this resemblance.

Anoxemia. The third precipitating factor of coronary insufficiency in pulmonary embolism is anoxemia. This is manifested clinically by dyspnea, tachypnea and cyanosis which result from obstruction of the pulmonary artery, diminished pulmonary blood flow and impaired oxygenation of the blood.

Anoxemia and asphyxia may produce anoxic changes in the myocardium of both the left and the right ventricles. In anoxemia arising from conditions other than pulmonary embolism, increase in coronary blood flow is provided by coronary vasodilatation,⁴⁰ but with pulmonary embolism the shock and right ventricular dilatation incident to the embolism produce absolute diminution of coronary blood flow. The effect of the anoxemia on the myocardium is thus intensified by the associated ischemia.

Anoxemia may be responsible for the electrocardiographic changes in pulmonary embolism particularly in the coronary insufficiency group, since the RS-T and T wave abnormalities produced by anoxemia and by coronary insufficiency are indistinguishable.^{12,13,41} Similar RS-T and T wave changes have been observed in acute cor pulmonale not due to pulmonary embolism, for example, in acute bronchial asthma. Many years ago it was reported⁴² that in animals identical electrocardiographic changes occurred in asphyxia, acute asthma and following clamping of the pulmonary artery. The changes in the RS-T segment and T waves which commonly occur during and immediately following an asthmatic paroxysm have been attributed to myocardial anoxia resulting either from diminished blood oxygen saturation⁴³ or from acute coronary insufficiency.⁴⁴ We have observed cases of bronchial asthma in which the severity and prolonged duration of the electrocardiographic changes suggested that the myocardial anoxia had produced myocardial infarction.

Pulmcoronary Reflexes. A fourth mechanism which may play a part in production of coronary insufficiency in pulmonary embolism is reflex coronary constriction mediated through the vagus nerve endings in the pulmonary arterial tree. There is no doubt that a reflex inhibitory effect on the heart may exert a considerable effect in pulmonary embolism⁷ and that it may produce slowing of the heart from sino-auricular depression and lowered blood pressure. However, evidence is lacking that such activity can cause coronary vasoconstriction.

SUMMARY

A study of forty-one consecutive fatal cases of pulmonary embolism confirmed by autopsy showed that acute coronary insufficiency is an important factor in determining the electrocardiographic and myocardial effects following embolism of the pulmonary artery. The electrocardiographic pattern of "acute cor pulmonale" (deep S₁ and Q₃, depressed RS-T in Lead

I, elevated RS-T in Lead III and T₃ inversion) occurred in only a minority of cases. In the majority the electrocardiographic changes were those characteristic of acute coronary insufficiency, namely, RS-T depression and T wave inversion in one or more leads and often in all leads.

Antecedent hypertensive or arteriosclerotic heart disease and cardiac hypertrophy were important predisposing factors of acute coronary insufficiency. The classical cor pulmonale pattern was seen more often in patients with previously normal hearts. When the electrocardiogram prior to the embolism was very abnormal, the electrocardiographic changes were usually those of coronary insufficiency or, less often, atypical in character. Furthermore, the presence of marked left axis deviation made the development of the cor pulmonale pattern less likely.

Right ventricular dilatation was not regularly associated with either "cor pulmonale" or "coronary insufficiency" electrocardiogram. The pattern of coronary insufficiency was often noted in patients with marked dilatation of the chambers of the right side of the heart, a fact which suggests that coronary insufficiency and right ventricular strain may occur simultaneously following massive embolism of the pulmonary artery.

Changes indicative of myocardial necrosis or infarction resulting from acute coronary insufficiency were found in ten cases or 24 per cent. In three of these cases there were gross changes in the myocardium and in seven cases histologic changes. Acute occlusion of a coronary artery was not seen in any of the hearts. The most frequent sites of necrosis were the subendocardial layer of the left ventricle and the papillary muscles. The anterior and posterior walls of the left ventricle were involved with equal frequency. The right ventricle was involved in only one case, emphasizing the greater deleterious effect of pulmonary embolism on the left ventricle. Acute myocardial changes were found in cases with electrocardiograms indicative of cor pul-

monale as frequently as in cases with electrocardiographic signs of acute coronary insufficiency.

Coronary insufficiency following embolism of the pulmonary artery is caused by diminished coronary blood flow and myocardial anoxia which result from systemic shock, right ventricular dilatation, anoxemia and possible reflex vasoconstriction. The pathologic physiology and relative importance of these factors are discussed.

REFERENCES

1. MCGINN, S. and WHITE, P. D. Acute cor pulmonale resulting from pulmonary embolism: its clinical recognition. *J. A. M. A.*, 104: 1473, 1935.
2. SCHIERF, D. and SCHOENBRUNNER, E. Ueber Herzbe-funde bei Lungenembolien. *Ztschr. f. klin. Med.*, 128: 455, 1935.
3. BARNES, A. R. Diagnostic electrocardiographic changes observed following acute pulmonary embolism. *Proc. Staff Meet., Mayo Clin.*, 11: 11, 1936.
4. LANGENDORF, R. and PICK, A. EKG-Befunde bei Lungenembolie. *Acta med. Scandinav.*, 90: 289, 1936.
5. LOVE, W. S., JR., BRUGLER, G. W. and WINSLOW, N. Electrocardiographic studies in clinical and experimental pulmonary embolization. *Ann. Int. Med.*, 11: 2109, 1938.
6. HORN, H., DACK, S. and FRIEDBERG, C. K. Cardiac sequelae of embolism of the pulmonary artery. *Arch. Int. Med.*, 64: 296, 1939.
7. DE TAKATS, G., BECK, W. C. and FENN, G. K. Pulmonary embolism: an experimental and clinical study. *Surgery*, 6: 339, 1939.
8. SOKOLOV, M., KATZ, L. N. and MUSCOVITZ, A. N. Electrocardiogram in pulmonary embolism. *Am. Heart J.*, 19: 166, 1940.
9. CURRENS, J. Electrocardiogram in pulmonary embolism. *Proc. Staff Meet., Mayo Clin.*, 17: 502, 1942.
10. CURRENS, J. and BARNES, A. R. The heart in pulmonary embolism. *Arch. Int. Med.*, 71: 325, 1943.
11. MURNAGHAN, D., MCGINN, S. and WHITE, P. D. Pulmonary embolism with and without acute cor pulmonale, with especial reference to the electrocardiogram. *Am. Heart J.*, 25: 573, 1943.
12. MASTER, A. M., DACK, S., GRISHMAN, A., FIELD, L. E. and HORN, H. Acute coronary insufficiency: an entity. Shock, hemorrhage and pulmonary embolism as factors in its production. *J. Mt. Sinai Hosp.*, 14: 8, 1947.
13. MASTER, A. M., GURNER, R., DACK, S. and JAFFE, H. L. Differentiation of acute coronary insufficiency with myocardial infarction from coronary occlusion. *Arch. Int. Med.*, 67: 647, 1941.
14. VIRGHOW, R. Neuer Fall von toedtllicher Embolie die Lungenarterien. *Arch. f. path. Anat. u. Physiol.*, 10: 225, 1856.
15. VILARIT, M., JUSTIN-BESANGON, L. and BARNIN, P. Physio-pathologie des accidents mortels consécutifs aux embolies pulmonaires. *Bull. et mém. Soc. mé. d. hôp. de Paris*, 52: 936, 1936.
16. MEGIBOW, R. S., KATZ, L. N. and FEINSTEIN, M. Kinetics of respiration in experimental pulmonary embolism. *Arch. Int. Med.*, 71: 536, 1943.
17. DUNN, J. S. The effects of multiple embolism of pulmonary arterioles. *Quart. J. Med.*, 13: 129, 1920.
18. HAGGARD, G. E. and WALKER, A. M. The physiology of pulmonary embolism as disclosed by quantitative occlusion of the pulmonary artery. *Arch. Surg.*, 6: 764, 1923.
19. GIBBON, J. H., JR., HOPKINSON, M. and CHURCHILL, E. D. Changes in circulation produced by gradual occlusion of the pulmonary artery. *J. Clin. Investigation*, 11: 543, 1932.
20. STEINBERG, B. and MUNDY, C. S. Experimental pulmonary embolism and infarction. *Arch. Path.*, 22: 529, 1936.
21. MEGIBOW, R. S., KATZ, L. N. and STEINITZ, F. S. Dynamic changes in experimental pulmonary embolism. *Surgery*, 11: 19, 1942.
22. KAUFFMANN, F. Kreislauf und Nervensystem. *Verhandl. d. deutsch. Gesellsch. f. Kreislauffsch.*, 6: 153, 1933.
23. RADNÉI, P. and MOSONYI, L. Ueber den gefäßverengernden pulmonocoronar Reflex. *Ztschr. f. d. ges. exper. Med.*, 98: 651, 1936.
24. HOCHREIN, M. and SCHNEYER, K. Der pulmocoronar Reflex. *Arch. f. exper. Path. u. Pharmacol.*, 187: 265, 1937.
25. MALINOW, M. R., KATZ, L. N. and KONDO, B. Is there a vagal pulmo-coro-nary reflex in pulmonary embolism? *Am. Heart J.*, 31: 702, 1946.
26. ECKHARDT, P. Zur Frage pulmocoronarer Reflexe bei Lungenembolie. *Arch. f. d. ges. Physiol.*, 241: 224, 1938-1939.
27. MENDLOWITZ, M. Experimental pulmonary embolism. *J. Thoracic Surg.*, 8: 204, 1938.
28. DALY, I., LUDONY, G., TODD, A. and VERNEY, E. B. Sensory receptors in the pulmonary vascular bed. *Quart. J. Exper. Physiol.*, 27: 123, 1937.
29. SCHWIEGK, H. Der Kreislaufkollaps bei der Lungenembolie. *Verhandl. d. deutsch. Gesellsch. f. Kreislauffsch.*, 11: 308, 1938.
30. PARIN, V. V. The role of pulmonary vessels in the reflex control of the blood circulation. *Am. J. M. Sc.*, 214: 167, 1947.
31. BUCHBINDER, W. C. and KATZ, L. N. The electrocardiogram in acute experimental distension of the right heart. *Am. J. M. Sc.*, 187: 785, 1934.
32. KRUMBHAAR, E. B. Note on electrocardiographic changes accompanying acutely increased pressure following pulmonary artery ligation. *Am. J. M. Sc.*, 187: 792, 1934.
33. WINANS, H. M., GOONE, J. V. and ASHWORTH, C. T. Ventricular strain: changes in the electrocardiogram produced by acute and chronic compression of the pulmonary artery. *South. M. J.*, 35: 225, 1942.
34. BUCHNER, F. Die Koronariinsuffizienz. P. 60. Dresden, 1939. Theodor Steinkopff.
35. FRIEDBERG, C. K. and HORN, H. Acute myocardial infarction not due to coronary artery occlusion. *J. A. M. A.*, 112: 1675, 1939.
36. DURANT, T. M., GINSBERG, I. W. and ROESLER, H. Transient bundle branch block and other electro-

- cardiographic changes in pulmonary embolism. *Am. Heart J.*, 17: 423, 1939.
37. FROMMEL, E. Les troubles du rythme cardiaque au cours de l'embolie pulmonaire mortelle. *J. de physiol. et de path. gén.*, 26: 247, 1928.
38. WHITE, P. D. The acute cor pulmonale. *Ann. Int. Med.*, 9: 115, 1935.
39. GREGG, D. E. Phasic blood flow and its determinants in right coronary artery. *Am. J. Physiol.*, 119: 580, 1937.
40. GREEN, H. D. and WEGRIA, R. Effects of asphyxia, anoxia and myocardial ischemia on the coronary blood flow. *Am. J. Physiol.*, 135: 271, 1942.
41. LEVY, R. L., WILLIAMS, N. E., BRUENN, H. G. and CARR, H. A. "Anoxemia test" in diagnosis of coronary insufficiency. *Am. Heart J.*, 21: 634, 1941.
42. CRIEP, L. H. Electrocardiographic studies of the effect of anaphylaxis on the cardiac mechanism. *Arch. Int. Med.*, 48: 1098, 1931.
43. MAINZER, F. and KRAUSE, M. Electrocardiogram in bronchial asthma paroxysm. *Cardiologia*, 5: 261, 1941.
44. HARKAVY, J. and ROMANOFF, A. Electrocardiographic changes in bronchial asthma and their significance. *Am. Heart J.*, 23: 692, 1942.

Auricular Fibrillation without Other Evidence of Heart Disease^{*}

A Cause of Reversible Heart Failure

EDWARD PHILLIPS, M.D. and SAMUEL A. LEVINE, M.D.

Los Angeles, California

Boston, Massachusetts

IT is now well known that auricular fibrillation may occur in people without other evidence of organic heart disease. This is particularly true of the paroxysmal form of the irregularity for transient spells are frequently seen in individuals who are otherwise well. Even persistent auricular fibrillation lasting for months or years without any other evidence of organic disease, subjective or objective, has been observed occasionally. What has not been sufficiently appreciated is that such patients occasionally develop outspoken congestive heart failure and that all evidence of heart disease may disappear with complete return to a normal state if the gross irregularity can be restored to normal rhythm. In this sense there is a small but definite group of patients with moderate to advanced heart failure in whom the entire process is reversible under appropriate therapy. Finally, there is a strong suspicion, from the experience to be discussed, that some patients with irreversible congestive heart failure and auricular fibrillation started with an essentially normal heart but because of prolonged auricular fibrillation developed cardiac enlargement and heart failure. Such patients then may partially respond to digitalis and diuretics. They may develop hypertension or other cardiac complications and succumb, as most patients with organic heart disease do; this is often called chronic myocarditis with auricular fibrillation or instances of non-

valvular heart disease. It is inferred that these eventualities might have been delayed or prevented if the original arrhythmia had been rectified early enough.

One of the first cases of auricular fibrillation with congestive failure without other evidence of organic disease was reported by Gossage and Hicks.¹ Although postmortem examination showed hypertrophy and dilatation of the left ventricle, the authors believed that the heart originally had no organic abnormalities and that the hypertrophy was a consequence of the arrhythmia. Parkinson and Campbell² found no evidence of heart disease in 30 of their 200 patients with paroxysmal auricular fibrillation. There was no apparent cause for the irregularities in eighteen, and infection or toxic agents were thought to be the precipitating factors in the other twelve cases. Auricular fibrillation eventually became chronic in three of their patients with normal hearts. Fowler and Baldridge³ reported seven cases of transient and three of persistent auricular fibrillation in young adults without evidence of heart disease. Mohler and Lintgen⁴ found no apparent cause for auricular fibrillation in about 6.5 per cent of their 220 patients. Likewise, Friedlander and Levine⁵ in 1934 reported thirty-five cases of auricular fibrillation and four of auricular flutter without evidence of heart disease. This comprised about 6 per cent of all their cases of auricular fibrillation. A similar group of forty-six cases of

^{*} From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass. This study was partly supported by the Anna R. Lown Cardiac Research Fund.

transient and three of chronic auricular fibrillation was published in 1936 by Orgain, Wolff and White.⁶ It is apparent that auricular fibrillation, either transient or permanent, without organic disease is not at all rare and may be expected to occur in a little more than 5 per cent of all fibrillators.

What is more important is that the irregularity may precipitate congestive failure when the heart is otherwise normal. Although this study is not concerned with the development of anginal pain following paroxysmal rapid heart action, such a complication does occur and has been thoroughly discussed by Wolff.^{7,8} In the case published by Gossage and Hicks¹ a twenty-three year old man developed progressive cardiac enlargement and chronic failure in spite of digitalization and died after running across a road eighteen and one-half months after the onset of his illness. Parkinson and Campbell's patient² was an athlete who developed paroxysmal fibrillation in 1912 at the age of twenty-four years. In 1920 the arrhythmia became permanent and two years later congestive failure appeared. At one time his life was saved by the intravenous administration of strophanthin, but he remained a cardiac invalid for the next three years despite digitalis therapy. In 1925 the cardiac mechanism was reverted to normal by quinidine which resulted in a complete recovery. Five years later the patient was engaging in vigorous sports without evidence of heart disease.

Brill⁹ reported the case of a forty-three year old female who developed auricular fibrillation in 1935. Ten weeks later cardiac enlargement and congestive failure developed. After reversion to normal rhythm with 0.2 Gm. of quinidine the heart size returned to normal and the congestive failure disappeared. Ten years later this patient was well, showing no evidence of heart disease.¹⁰ Trotter and Eden¹¹ reported the case of a forty-three year old man in whom auricular fibrillation without apparent cause produced congestive failure.

Digitalis reverted the rhythm to normal and cured the heart failure. Seven years later permanent auricular fibrillation developed and within several months congestive symptoms recurred and could not be controlled adequately with digitalis. After total thyroidectomy, which was performed as a last resort, normal rhythm returned and all the symptoms disappeared. There was no gross or microscopic evidence of thyrotoxicosis in the gland.

Levine and Beeson¹² reported an instance in which severe congestive failure occurred after auricular fibrillation became permanent when there was no other evidence of heart disease. This patient was also cured by reversion to normal rhythm. (Case II.) It is evident from these isolated case reports that severe heart failure may be completely reversible in a small group of patients in which auricular fibrillation *per se* is the cause of the disability.

The purpose of this study was to investigate some of the changes in the dynamics of the circulation that appear to develop as a result of auricular fibrillation in patients who have no other evidence of heart disease, and to emphasize that the arrhythmia alone can be the cause of congestive heart failure. The clinical evidence brought forth also suggests that some cases of irreversible heart failure with auricular fibrillation may have started with an essentially sound heart and that the subsequent disability might have been prevented if normal rhythm had been restored by use of quinidine in the early stages of the arrhythmia.

ABNORMAL CIRCULATORY DYNAMICS IN AURICULAR FIBRILLATION

There is abundant evidence, both clinical and experimental, that auricular fibrillation produces deleterious effects on the circulation. Stewart and his co-workers^{13,14} and Blumgart and Weiss^{15,16} showed that the rate of blood flow was slowed in auricular fibrillation by 20 to 68 per cent. The cardiac output was also found decreased.^{17,18} Impairment of the circulation could not be ascribed to the increased heart rate for the

cardiac output and rate of blood flow in dogs were found unchanged in regular tachycardia but decreased in auricular fibrillation although the ventricular rates were the same.^{14,17} After resumption of normal rhythm the rate of blood flow in dogs returned to normal,¹⁴ and the circulation time in patients decreased by an average of 8 seconds.¹⁵ Landis and his co-workers¹⁹ found a disproportionate rise in central venous pressure after exercise in dogs with auricular fibrillation.

The size of the heart may also be affected by the fibrillating state. Stewart and his co-workers found a decrease in heart size in seven patients after cessation of auricular fibrillation.¹⁸ In one of these, previous digitalization resulted in only a slight decrease in heart size. Stewart and Crawford²⁰ showed that the size of a dog's heart may increase in auricular fibrillation while it remains unchanged or becomes smaller in regular tachycardia. Levine and Golden²¹ inferred that dilatation of the heart in patients with regular tachycardias depends upon duration of the attack, rapidity of the ventricular rate and original health of the heart. Since auricular fibrillation is more prone to cause cardiac enlargement than a rapid regular rhythm of the same rate,²⁰ it is to be expected that enlargement will occur with slower irregular ventricular rates than in the reported cases of dilatation in regular tachycardias.

A further factor that is often insufficiently appreciated is the effect of effort on the circulatory state when auricular fibrillation is present. Although digitalis may lower the ventricular rate in auricular fibrillation to normal during rest and restore almost normal circulatory dynamics at rest, it does not protect the ventricles from a disproportionate rise in rate with exercise. Blumgart²² showed that in auricular fibrillation not only was the rise in ventricular rate with exercise greater than in the normal, but that there was a delay in return to normal with rest even in the digitalized patient. In these cases, when normal rhythm was restored by quinidine, there was less ac-

celeration of the ventricles in response to effort.

In the case reports just cited and in some of those to be discussed, it has been noted that treatment with digitalis alone was not adequate to control the symptoms of heart failure. Restoration to normal rhythm following quinidine was found to result in a complete cure in an appreciable number of instances. Such clinical observations are consistent with the experimental data just cited and refute some earlier opinions that the circulatory dynamics in well controlled auricular fibrillation are normal.²³

Clinical Material. This study is based on a review of eighty-four patients with auricular fibrillation who were regarded as having no other evidence of organic heart disease. Fifty-eight of these were seen in private practice and the other twenty-six were observed only at the Peter Bent Brigham Hospital. Of the total there were fifty-three who were intimately observed in the hospital and of these, forty-seven were carefully studied during arrhythmia and after reversion to a normal mechanism. There were seventy-three males and eleven females in the entire series. The average age was fifty years, and the range was from twenty-three to sixty-seven years. Only ten were over sixty years of age and twenty were under forty. Seven of these patients had frank congestive failure and will be reported in detail later. There were seven others who had latent heart failure. Evidence for this was generally reflected in a distinct lowering of the vital capacity of the lungs, a somewhat slower velocity of blood flow (both of which improved after treatment) and dilatation of the heart.

Symptoms. Palpitation was the most common chief complaint. Sixty-five of these patients complained of this sensation at one time or another. It is of some interest that there were nineteen instances in which palpitation was absent when fibrillation had occurred. Other primary complaints were weakness (twenty-five cases), breathlessness (twenty-three cases), syncope (thirteen cases)

and nervousness (eight cases). Other major symptoms present in isolated instances were dizziness, ankle edema and chest pain. Anginal pain on effort was present in three patients. Dyspnea and weakness were the most prominent symptoms in the patients with congestive failure.

Duration. In this study auricular fibrillation was regarded as permanent if it lasted more than seven days. There were twenty-three patients who had typical transient bouts of auricular fibrillation although in eight of these the arrhythmia had lasted one to seven days when treatment was instituted. These transient episodes covered varying periods of time, in different patients, from one month to ten years. The frequency of recurrences also varied greatly from extremely rare episodes to those that recurred every few weeks or more often. The other sixty-one patients in the series all had permanent auricular fibrillation. Detailed observations concerning the duration of auricular fibrillation were made on those fifty-three patients that were intimately studied in the hospital. The others were treated at home or in various other hospitals, and some were not treated at all or refused treatment. There were thirteen with a duration of eight days to one month, thirty of one to twenty-four months' duration, four of two to three years' duration and six of more than three years, the longest being nine years. Twenty of those with permanent auricular fibrillation had previous transient attacks lasting hours or several days over a period of one to twenty-three years before they were seen. Four of these twenty had previous persistent fibrillation which had been successfully reverted elsewhere by the use of quinidine.

The average duration of auricular fibrillation in the forty-six patients without frank congestive failure was 12.2 months at the time treatment was started, the range being from one month to nine years. The average duration in the seven patients with congestive failure was 3.7 months, and that of seven with latent failure was 11.3 months. It is evident, therefore, that duration of the

arrhythmia was not a significant factor in the development of heart failure. It is of interest that in the group of thirteen patients in whom the arrhythmia persisted, either because no treatment was given or because treatment failed, the known average duration of auricular fibrillation was 10.6 years. This does not include an instance in which the irregularity probably was present for forty-four years.

Associated Conditions. None of the eighty-four patients had a past history of rheumatic fever or manifested any evidence of rheumatic heart disease. None had any acute infection at the time of examination. Routine urine analyses and blood counts were essentially normal. The blood Wassermann was determined in sixty-three patients. One had well treated asymptomatic syphilis of the central nervous system, two had doubtful reactions without stigmas of lues and the remaining all had negative serologic reactions. Chronic cholecystitis and cholelithiasis were present in four patients. Other conditions, like renal stones, pulmonary emphysema, etc., were rare and not regarded as related to the arrhythmia. The only specific etiologic factors that might be incriminated in the initiation of the fibrillation in a few instances was alcohol and in one instance an excessive amount of privine used in the form of nose drops. In general it appeared that the arrhythmia was not due to infection, toxic influences or associated diseases and had to be regarded as of unknown or of neurogenic origin.

Heart Murmurs. Cardiac murmurs were striking by their absence. Only six patients of the entire eighty-four had a faint grade I, and one additional patient had a grade II apical systolic murmur. Three of these murmurs occurred in patients with congestive failure. The murmurs disappeared in these three and in one of the others when the rhythm was regularized. There were no other auscultatory abnormalities except for the arrhythmia.

Blood Pressure Observations. The average blood pressure of the entire series was 128/80. The highest was 150/100 during

arrhythmia which fell to 126/90 when the rhythm became regular. Only seven had readings above 145/90. There was no difference between the pressure levels with or without congestive failure. The average blood pressure in eleven patients who had determinations before and after reversion was 145/89 during auricular fibrillation and 133/80 when the rhythm became regular. It is concluded that there was no essential hypertension in this series of patients.

X-ray Findings. Seven-foot heart films were made in twenty patients without frank congestive failure during auricular fibrillation and within forty-eight hours after normal rhythm was restored. The interval between the two comparable films was generally only several days. In none of these cases was the heart regarded as significantly enlarged. The average diameter of the heart was 14.4 cm. during arrhythmia and 14.3 cm. after regularization. In three cases the transverse diameter decreased 0.9 cm., 1.4 cm. and 1.0 cm., respectively. In the first there was no evidence of cardiac incompetency during fibrillation. In the second the vital capacity increased 900 cc. when the rhythm became regular, and in the third the circulation time was 26 seconds (decholin) during fibrillation. There was a fourth instance in which no change in heart size was detected directly after reversion although one year later it had decreased 0.8 cm. In this case it required fourteen days to accomplish regularization, during most of which time auricular flutter with a rapid ventricular rate was present. The vital capacity of the lungs rose from 2,400 cc. to 3,700 cc. when the rhythm became regular. Twenty years later this patient was well and had no evidence of heart disease. The latter three of the aforementioned four patients are presumed to have had slight cardiac dilatation and latent congestive failure while they were fibrillating.

Heart films were obtained during and within forty-eight hours after arrhythmia in four of the seven patients with frank congestive failure. The average diameter of the heart in these cases before and after

regularization was 17.4 cm. and 15.4 cm., respectively. In one patient, although there was enlargement, no decrease occurred. In two instances the size of the heart became normal and showed a decrease of 3.6 and 4.0 cm. In the fourth patient the heart size decreased 0.9 cm. one day after regularization and there was a further decrease of 2.0 cm. nineteen months later. The only patient with congestive failure who showed no decrease in heart size had had seventy-three attacks of auricular fibrillation (some of them prolonged) in twenty-one years. The irreversible cardiac hypertrophy in this sixty-five year old man was probably the result of long sustained auricular fibrillation. The general contour of the cardiac silhouette in those patients showing enlargement was not remarkable and was regarded as representing for the most part reversible dilatation caused by the arrhythmia. In the larger group without heart failure it is significant that neither the left nor right auricle was enlarged by fluoroscopy.

Electrocardiographic Observations. Electrocardiograms were made in all (eighty-four) patients during fibrillation and within one to several days after the auricular fibrillation disappeared. In most cases the tracing was obtained within twenty-four hours. Left axis deviation was present in eighteen patients. None showed right axis deviation. Six patients* showed prolongation of the P-R interval from 0.22 to 0.28 seconds, nine had premature auricular beats and two had both auricular and ventricular premature beats after reversion. In no case were the extrasystoles frequent or troublesome. Three patients without failure showed transient inversion of the T waves in leads II and III, and one with heart failure had transient inversion of the T waves in leads I and II following reversion. It appears that transient prolongation of the P-R interval is not uncommon after cessation of auricular fibrillation. Changes in the T waves have often been observed after reversion of supraventricular or ventricular tachycardia.²⁴⁻²⁷ Minor abnormalities in the tracings might

*One reverted spontaneously without any medication

be confused with those seen in myocardial infarctions but they were not accompanied by any alteration in the QRS complex. Furthermore, the T wave changes may be partly the result of digitalis or quinidine for in most cases one or the other of these two drugs were employed. These T wave changes cannot always be attributed to drug effect for in one of our patients in whom reversion occurred spontaneously without any medication there was transient inversion of the T wave in leads II and III.

Basal Metabolism Determinations. There was no clinical evidence of thyrotoxicosis in any case. The basal metabolic rate was determined in fifty-six of these patients. The readings varied from -20 per cent to +10 per cent except for one instance of +20 per cent (during heart failure). The average reading was -7.2 per cent. In a certain number of instances repeat determinations obtained after reversion showed no significant difference. It can safely be assumed that these patients were not suffering from hyperthyroidism.

Vital Capacity of the Lungs. For the most part the vital capacity of the lungs was essentially normal in those patients without heart failure and showed only a slight increase after reversion. There were a few exceptions however. Determinations were made in twenty-eight patients during the arrhythmia and one day after the rhythm was regularized. The average figures for the two occasions were 3,448 cc. and 3,700 cc., respectively. There were three instances of abnormally low readings which showed increases of 900, 1,300 and 1,300 cc. when reversion took place. In the group with heart failure the average vital capacity was 2,575 cc. before and 3,725 cc. after reversion. When a marked increase takes place, it is a fair indication that some congestive failure had been present.

Circulation Time. The arm-to-tongue circulation time was measured during arrhythmia and again within forty-eight hours after the rhythm became regular in eleven patients without congestive failure. The circulation time with decholin in seven patients

varied from 15 to 26 seconds (average 21 seconds) during auricular fibrillation and from 16 to 23 seconds (average 18 seconds) with normal rhythm. The circulation time in the other four patients varied from 19 to 39 seconds (average 29 seconds) with magnesium sulfate during arrhythmia and from 19 to 30 seconds (average 24 seconds) with normal rhythm. Four patients showed significant reductions in circulation times of 6, 6, 8 and 16 seconds, respectively, with normal rhythm. Similar measurements were made during and after arrhythmia in only two patients with heart failure. The rate was 33 and 22 seconds during auricular fibrillation and fell to 14 and 20 seconds, respectively, with normal rhythm. In general it would seem that the velocity of blood flow accelerates somewhat after reversion, particularly in patients who previously had heart failure.

Venous Pressure. The venous pressure (method of Lyons, Kennedy and Burwell)³² was determined in thirteen patients during auricular fibrillation and again within forty-eight hours after the rhythm became regularized. It varied from 60 to 170 mm. H₂O, averaging 107 mm. H₂O during the period of auricular fibrillation. When the rhythm was regular, the venous pressure averaged 97 mm. H₂O with a range of 55 to 145 mm. H₂O. Only two patients had elevated venous pressures (170 and 160 mm. H₂O) during the period of auricular fibrillation; with normal rhythm their venous pressures fell to 140 and 145 mm. H₂O, respectively. The venous pressure was 180 and 130 mm. H₂O in two patients with congestive failure during arrhythmia. When the rhythm became regular, it dropped to 150 and 45 mm., respectively. As with other criteria of circulatory dynamics the venous pressure tended to be slightly elevated in those with some failure and returned to normal after treatment.

TREATMENT

There were sixty-two episodes of auricular fibrillation in this study occurring in fifty-three individuals who received quinidine

therapy. Digitalis was administered to all patients with rapid ventricular rates in order to slow the rate. In only one instance was regularization obtained and that occurred a few hours after 1.2 mg. of digitoxin was given orally. In general the routine of administering quinidine was to give three oral doses daily at four-hour intervals, starting with an initial dose of 0.2 Gm. and increasing each by the amount of 0.1 or 0.2 Gm. In rare instances the patient received four doses a day, and the interval between doses in two patients was two rather than four hours. In our early experience when the three daily doses were identical and increases were made each day rather than in each dose it took longer to obtain reversion. Patients were examined just before each dose of quinidine was administered for if regularization had been obtained by the previous dose the amount of the drug would be decreased to a maintenance dose of 0.2 Gm. two or three times a day rather than increased.

Four patients reverted promptly after the first dose of 0.2 Gm. Four others reverted after the second dose (0.3 Gm.). In thirteen instances regularization occurred after the third dose (0.4 Gm.). Only fourteen patients required doses in excess of 0.7 Gm. In eight the amount had to be gradually increased to single doses of 1.0 to 1.5 Gm. In one case reversion took place after five individual doses of 1.0 Gm. each, and in another after three individual doses of 1.1 Gm. In the final patient regularization did not occur until a dose of 1.5 Gm. was reached. Although the number of patients with congestive failure was not great (seven cases), the dose required for regularization was somewhat larger than in those without heart failure. However, in both groups small doses were adequate in some and very large doses were necessary in others. There were seven failures in the treatment of sixty-two different attacks of fibrillation, i.e., 88.5 per cent successes. In three young men, aged thirty-two, thirty-seven and thirty-nine years, treatment was unsuccessful after individual doses of 0.9,

2.0 and 1.5 Gm., respectively. A fourth was a man sixty years of age who twice before responded satisfactorily to quinidine therapy but finally was refractory even to doses of 1.0 and 1.2 Gm. In a fifth case treatment had to be discontinued after a dose of 0.5 Gm. because of marked nausea and ringing in the ears. Another forty-seven year old man developed auricular flutter and failed to become regular despite a dose of 1.0 Gm. (Case vii.) The last patient was a sixty-seven year old man who responded favorably to quinidine many times in the past but finally failed to revert on increasing doses up to 1.5 Gm. This patient was even given 1.2 Gm. intravenously without success. A short time later regularization did occur at another hospital but the dosage employed is not known. (Case v.) In all cases in which the arrhythmia persisted after quinidine therapy a proper maintenance dose of digitalis was given. The previous duration of the irregularity did not have any significant influence upon the ease with which normal rhythm could be restored or the dose of quinidine required. It is evident that as a group these patients have a high incidence of favorable response to quinidine (88.5 per cent) and that only small or moderate doses were required in most cases. It is obvious, however, that some of the most satisfactory results were obtained only when very large doses were employed. This experience is in striking contrast to the results obtained in the treatment of mitral stenosis and auricular fibrillation. In that condition regularization following quinidine cannot be expected to occur in more than one-third to one-half of the cases.

Toxic Reactions and Complications. Worrisome toxic reactions with quinidine were very uncommon in this group of patients. With the large doses that were used in some of the patients, there was often a feeling of slight nausea, weakness and buzzing in the ears. These symptoms did not interfere with our therapy nor did they inhibit us from continuing quinidine if it seemed indicated. There was one patient that went into shock after receiving five 1 Gm. doses

of the drug. In fact, it seemed as if his heart had actually stopped. The patient had a convulsion but normal rhythm was quickly resumed with complete recovery. (Case II.) One woman, fifty-five years old, had a mild left hemiparesis forty-eight hours after resumption of normal rhythm. Complete recovery took place four days later. A diagnosis of questionable embolism was made. A third patient had a transient erythematous macular rash forty-eight hours after the last dose of quinidine. Auricular flutter developed in ten patients during quinidine therapy. In seven of these patients normal rhythm was eventually resumed and in three auricular fibrillation returned and persisted. It is striking that serious complications were practically absent so that quinidine therapy can be regarded as a safe procedure in the group of patients with auricular fibrillation who had no significant heart disease.

PROGNOSIS

The prognosis in this group was quite good. There were seventy-one patients in whom adequate follow-up information was available. Of the fifty-three intimately studied in the hospital only six subsequently died. One patient had a recurrence of auricular fibrillation after maintaining a regular rhythm for three years. No attempt at re-regularization was made. One and one-half years later he developed angina pectoris and died six months after this at the age of fifty-five. (Case III.) Two others relapsed into auricular fibrillation and died of an unknown cause one and two years later at the ages of sixty-nine and sixty-one years, respectively, having first manifested gross irregularity six and four years before death. Two patients died of cancer at the age of sixty and sixty-three, the first twelve and one-half years and the other six months after reversion to regular rhythm. The sixth died as the result of an automobile accident one month after quinidine therapy.

In addition, there were five deaths among the thirty-one other patients. One was shot

three years after the onset of arrhythmia. Another man died at the age of forty-one from angina pectoris which he had for six months, seventeen years after the onset of auricular fibrillation. A third died of cerebral hemorrhage eight years after fibrillation was first noted. Autopsy did not reveal any embolism. The other two patients died of cerebral emboli at the ages of fifty-two and sixty after thirty-one years and five and one-half years, respectively, of chronic auricular fibrillation. Considering the large number of patients, especially males, involved in this study it is not surprising that there have been a small number of cardiovascular fatalities such as those due to coronary or cerebral vascular disease. This would necessarily be true of any group of adults followed well into the second half of life. The one cardiac complication that might be directly related to the presence of auricular fibrillation would be emboli coming from auricular mural thrombi. We have no case of this sort that has been confirmed postmortem. The two instances in which the clinical diagnosis of cerebral embolism was made afford presumptive evidence that thrombi may develop in the left auricle in these cases. If this is so, the evidence presented indicates that it must be a rare phenomenon.

The average duration of life among the sixty living patients is 10.0 years from the beginning of the cardiac arrhythmia. The average age of these patients when last heard from was 56.0 years. During this period of observation there was no known instance of thyrotoxicosis. One patient developed coronary thrombosis at the age of fifty-two from which he recovered. This illness occurred four years after a recurrence of persistent auricular fibrillation. He was doing well although still fibrillating two years later. Another patient began to show evidence of congestive failure while in persistent fibrillation but responded to cardiac therapy and is still able to do a moderate amount of work as a farmer two years later. A final patient (Case VII) had hemiplegia two years after the onset of

auricular fibrillation which did not respond to quinidine. The striking feature is the absence of either heart failure or any other significant cardiac disability except palpitation in most of these patients.

DURATION OF REGULAR RHYTHM

Among the patients observed intimately in the hospital there were forty-seven in whom regularization was obtained. Adequate follow-up information was available in forty-three. Twenty-five of them were fifty years or older and eighteen were under fifty years. Nineteen of the older group relapsed into auricular fibrillation; nine did so within one year, but the average duration of normal rhythm before relapse in this group was twenty-one months. In the younger group only five of eighteen patients relapsed, and the average duration of normal rhythm before relapse was 61.4 months. Only one of this group relapsed within one year. The average duration of regular rhythm in the entire group that did relapse was 26.9 months. It is evident from this analysis that the duration of regular rhythm is much longer in the younger than in the older patients.

Another factor that seemed to influence the duration of regular rhythm was the length of time auricular fibrillation had previously been present. In the group in which the irregularity persisted for over one year regularization lasted an average period of 15.6 months. When fibrillation had been present less than one year, the subsequent period of regular rhythm was 35.1 months. These figures only pertain to those who reverted to the irregularity. There were nineteen patients who maintained a regular rhythm throughout the period of observation. Only two of them had had auricular fibrillation for more than one year and all but five were under fifty years of age. It is of interest that one patient has maintained a regular rhythm for twenty-one years since reversion. It follows, therefore, that the shorter the period of irregularity the longer the period of regular rhythm.

COMMENT

All the factors which lead to heart failure in patients with auricular fibrillation but without evidence of organic heart disease are not known. The duration of auricular fibrillation did not appear to be the determining factor. Friedlander and Levine³ reported four such cases of permanent auricular fibrillation of nine and thirty-one years' duration in which no evidence of heart failure was present. One of these patients has had this gross arrhythmia now for twenty-seven years. It started at the age of twenty-two, and for the following fifteen years he received no cardiac medication whatever although the ventricular rate was moderately rapid. He always refused to try quinidine. In 1935 during the course of lobar pneumonia the ventricular rate rose to 185. He was then digitalized and has taken a maintenance dose of 0.1 Gm. of digitalis leaf daily ever since. There has never been any evidence of heart failure. This patient is able to do hard work without difficulty at the present time. During the past twenty years the vital capacity of the lungs decreased from 4,300 cc. to 3,600 cc. There were three other patients in this present study who were known to have had persistent auricular fibrillation for fifteen years without complications, and another instance in which it was judged from the history that the arrhythmia had persisted for forty-four years without producing cardiac failure.

It is of further interest that frank congestive failure did not occur in any patient with auricular fibrillation of more than one year's duration, but there were two instances in which latent congestive failure was present when the irregularity lasted three years. In all seven instances of frank failure and in five of the seven cases of latent heart failure the irregularity lasted only weeks or months. It would appear that if heart failure is to develop it does so comparatively soon after the irregularity first appears if it persists.

The actual ventricular rate seems to have a definite influence on the development of heart failure in these cases. The average ventricular rate before digitalis therapy in those with frank failure was 146 (ranging from 122 to 170), in those with latent failure 119 (ranging from 100 to 134) and in those without failure 100 (ranging from 72 to 160). Only two of the latter group had heart rates over 118.

It is impossible to predict how long normal rhythm will persist in any given patient. The ease with which the patient reverted to normal rhythm on quinidine was no index to the duration of regular rhythm. Fifty per cent of those who responded favorably after one to three doses of quinidine went back into auricular fibrillation within six months. In contrast, one patient who required three doses of 1.1 Gm. each had no recurrence of arrhythmia in the subsequent twenty-one years.

In appraising the value of regularization of the heart by use of quinidine one naturally would have to consider the risk of the procedure, duration of the regular rhythm once it had been obtained and improvement in the general health of the patient. In this group of cases under consideration there were no untoward results. One may conclude that the risk was negligible. The duration of regular rhythm was sufficiently long to make one believe that therapy was worth while. The average duration of normal rhythm will obviously become longer and longer because many patients are still continuing with a normal heart rhythm for years. Finally, the group that had congestive failure was obviously helped tremendously as they were restored to good health. The same was true to a less dramatic degree in those who had latent failure. The experience with the latter two groups of cases lead us to the opinion that development of heart failure was prevented by regularization of the rhythm in some of the other patients who were well compensated and essentially asymptomatic.

A certain number of patients are encountered in practice who have auricular

fibrillation and cardiac enlargement without apparent cause. These are often diagnosed as "heart disease of unknown etiology" or as "chronic myocarditis." Perhaps if the blood pressure is slightly elevated the case is designated as hypertensive heart disease. In time, irreversible cardiac enlargement and chronic congestive failure lead to death. We believe that many such cases originally were instances of auricular fibrillation without significant heart disease. Our six cases of frank congestive failure which were reverted to normal rhythm would undoubtedly have remained in chronic congestive failure on digitalis therapy and considered as examples of "chronic myocarditis." Restoration of normal rhythm abolished the congestive failure and revealed an essentially normal heart. The seven patients with latent congestive failure also illustrate the same sequence. Progressive cardiac enlargement and congestive failure would probably have developed and become irreversible if the auricular fibrillation had been allowed to persist. It is obvious that auricular fibrillation cannot be assumed to be due to organic heart disease. Such an attitude might make the physician fearful of using quinidine and condemn these patients to chronic invalidism and eventually to a cardiac death when the condition might have been prevented early in its progress or corrected even after it had become fairly well advanced.

SUMMARY AND CONCLUSIONS

1. Eighty-four patients with auricular fibrillation of unknown etiology who had no evidence of organic heart disease were studied. Sixty-one had permanent fibrillation and twenty-three had transient fibrillation. Eighty-seven per cent of these were males. The average age was fifty years, ranging from twenty-three to sixty-seven years. The average blood pressure was 128/80. The average basal metabolic rate was -7.2 per cent.

2. Forty-seven patients were studied carefully before and after reversion of the

arrhythmia with quinidine. Six had marked congestive failure. A seventh patient who did not respond to quinidine also had congestive failure. Seven others had latent congestive failure.

3. The most common symptom of those without failure was palpitation. In the group with failure the customary features of dyspnea, orthopnea and an enlarged liver were present.

4. The transverse diameter of the heart averaged 14.4 cm. during fibrillation and 14.3 cm. after reversion in twenty patients without frank failure. The transverse diameter in four cases of congestive failure averaged 17.4 cm. during and 15.4 cm. after auricular fibrillation.

5. Six patients had slight prolongation of the P-R interval after reversion. One of these reverted spontaneously without any medication. Four patients showed transient inversion of T waves after reversion, one of which reverted spontaneously without any medication.

6. The vital capacity of the lungs averaged 3,448 cc. in twenty-eight patients without failure during auricular fibrillation and 3,700 cc. after reversion. In the group with failure the vital capacity increased from 2,575 to 3,725 cc.

7. The arm-to-tongue circulation time in eleven patients without failure averaged 24 seconds during auricular fibrillation and 20 seconds after regularization.

8. The venous pressure averaged 107 mm. H₂O in thirteen patients without failure during auricular fibrillation and 97 mm. H₂O after reversion.

9. Regularization following quinidine occurred in 88.5 per cent of the patients and there were no untoward complications. In those that did relapse the normal rhythm persisted on the average for 26.9 months. The average duration of regular rhythm in patients under fifty years who relapsed was 61.4 months; in those over fifty it was twenty-one months. Nineteen patients have not relapsed and still have regular rhythm after two months to twenty-one years. This maintenance of regular rhythm is much

longer than in patients with organic heart disease who were reverted with quinidine.

10. In the group showing advanced congestive heart failure, dramatic therapeutic responses were obtained, all symptoms and signs of heart failure disappearing after regularization.

11. It is concluded that auricular fibrillation *per se* may produce cardiac dilatation and progressive congestive failure in patients with otherwise normal hearts. This is a truly reversible type of heart failure.

12. There is reason to believe that a considerable number of patients with auricular fibrillation, cardiac enlargement and congestive failure (that eventually becomes irreversible) have little or no organic heart disease. We are also of the opinion that regularization of the rhythm with quinidine in the early stages may prevent progressive heart failure and in the latter stages may even be curative.

REFERENCES

1. Gossage, A. M. and Hicks, J. A. B. On auricular fibrillation. *Quart. J. Med.*, 6: 435, 1912-13.
2. Parkinson, J. and Campbell, M. Paroxysmal auricular fibrillation. A record of two hundred patients. *Quart. J. Med.*, 24: 67, 1930.
3. Fowler, W. M. and Baldringe, C. W. Auricular fibrillation as the only manifestation of heart disease. *Am. Heart J.*, 6: 183, 1930.
4. Mohr, H. K. and Lintgen, C. Auricular fibrillation. An analysis of 220 cases. *Pennsylvania M. J.*, 35: 68, 1931.
5. Friedlander, R. D. and Levine, S. A. Auricular fibrillation and flutter without evidence of organic heart disease. *New England J. Med.*, 211: 624, 1934.
6. Orgain, E. S., Wolff, L. and White, P. D. Uncomplicated auricular fibrillation and auricular flutter. Frequent occurrence and good prognosis in patients without other evidence of cardiac disease. *Arch. Int. Med.*, 57: 493, 1936.
7. Wolff, L. Angina pectoris (or status anginosus) and cardiac asthma induced by paroxysmal auricular fibrillation and paroxysmal tachycardia. The value of quinidine sulphate in the treatment of these conditions. *New England J. Med.*, 208: 1194, 1933.
8. Wolff, L. Clinical aspects of paroxysmal rapid heart action. *New England J. Med.*, 226: 640, 1942.
9. Brill, I. C. Auricular fibrillation with congestive failure and no other evidence of organic heart disease. *Am. Heart J.*, 13: 175, 1937.
10. Brill, I. C. Congestive heart failure arising from uncontrolled auricular fibrillation in the otherwise normal heart. *Am. J. Med.*, 2: 544, 1947.

11. TROTTER, W. R. and EDEN, K. C. Total thyroidectomy for heart failure: an unusual case. *Brit. Heart J.*, 3: 200, 1941.
12. LEVINE, S. A. and BEESON, P. B. The Wolff-Parkinson-White syndrome, with paroxysms of ventricular tachycardia. *Am. Heart J.*, 22: 401, 1941.
13. STEWART, H. J. Observations on the blood gases in auricular fibrillation and after the restoration of the normal mechanism. *Arch. Int. Med.*, 31: 871, 1923.
14. STEWART, H. J., CRAWFORD, J. H. and HASTING, A. B. The effect of tachycardia on the blood flow in dogs. I. The effect of rapid irregular rhythms as seen in auricular fibrillation. *J. Clin. Investigation*, 3: 435, 1926.
15. BLUMGART, H. L. and WEISS, S. Clinical observation on the velocity of blood flow in auricular fibrillation and emphysema. *Tr. A. Am. Physicians*, 41: 294, 1926.
16. BLUMGART, H. L. and WEISS, S. Studies on the velocity of blood flow. IV. The velocity of blood flow and its relation to other aspects of the circulation in patients with arteriosclerosis and in patients with arterial hypertension. *J. Clin. Investigation*, 4: 173, 1927.
17. STEWART, H. J. and GILCHRIST, A. R. Studies on the effect of cardiac irregularity on the circulation. II. The estimation of cardiac output in dogs subject to artificial auricular fibrillation. *J. Clin. Investigation*, 5: 335, 1928.
18. STEWART, H. J., DEITRICK, J. E., CRANE, N. F. and THOMPSON, W. P. Studies of the circulation in the presence of abnormal cardiac rhythms. *J. Clin. Investigation*, 17: 449, 1938.
19. LANDIS, E. M., BROWN, E., FAUTEUX, M. and WISE, C. Central venous pressure in relation to cardiac "competence," blood volume and exercise. *J. Clin. Investigation*, 25: 237, 1946.
20. STEWART, H. J. and CRAWFORD, J. H. The effect of regular and irregular tachycardias on the size of the heart. *J. Clin. Investigation*, 3: 483, 1927.
21. LEVINE, S. A. and GOLDEN, R. Some observations on paroxysmal rapid heart action with special reference to roentgen-ray measurement of the heart in and out of attacks. *Arch. Int. Med.*, 29: 836, 1922.
22. BLUMGART, H. The reaction to exercise of the heart affected by auricular fibrillation. *Heart*, 11: 49, 1924.
23. KOHN, C. M. and LEVINE, S. A. An evaluation of the use of quinidine sulfate in persistent auricular fibrillation. *Ann. Int. Med.*, 8: 923, 1935.
24. CAMPBELL, M. Inversion of T waves after long paroxysms of tachycardia. *Brit. Heart J.*, 4: 49, 1942.
25. CURRIE, G. M. Transient inverted T waves after paroxysmal tachycardia. *Brit. Heart J.*, 4: 149, 1942.
26. GEIGER, A. J. Electrocardiograms simulating those of coronary thrombosis after cessation of paroxysmal tachycardia. *Am. Heart J.*, 26: 555, 1943.
27. COSSIO, P., VEDOYA, R. and BERCONSKY, I. Modifications of the electrocardiogram following certain attacks of paroxysmal tachycardia. *Rev. argent. de cardiol.*, 11: 164, 1944.
28. ZIMMERMAN, S. L. Transient T-wave inversion following paroxysmal tachycardia. *J. Lab. & Clin. Med.*, 29: 598, 1944.
29. EISAMAN, J. L. Electrocardiogram simulating posterior myocardial infarction after cessation of paroxysmal tachycardia. *Am. Heart J.*, 30: 401, 1945.
30. WARD, L. S. Abnormal electrocardiogram following recovery from paroxysmal tachycardia. *Am. Heart J.*, 31: 645, 1946.
31. STEEN, R. E. Paroxysmal tachycardia followed by temporary inversion of the T waves. *Brit. Heart J.*, 9: 81, 1947.
32. LYONS, R. H., KENNEDY, J. A. and BURWELL, C. S. Measurement of venous pressure by direct method. *Am. Heart J.*, 16: 675, 1938.

Case Reports will be included in the reprint.

Function of the Kidney and Metabolic Changes in Cardiac Failure^{*}

ELLIOT V. NEWMAN, M.D.

Baltimore, Maryland

THE purpose of this paper is to present and discuss some studies designed to describe the functional alterations of the kidney in cardiac failure.

It has long been known that in congestive failure with edema the excretion of sodium chloride is impaired and that the kidney function, as measured by less precise clinical tests, is diminished. During the years preceding the application of the more precise tests of renal function the kidney was assigned a secondary role in the pathogenesis of edema. According to Starling's conceptions, an increased extravasation of fluid through the peripheral capillary membrane due to increased venous back pressure from the failing heart was considered the primary cause of edema.¹ However, in his lectures in 1908 Starling surmised that the failing heart with low output would lead to peripheral splanchnic constriction and that the reduced flow to the kidney would lessen the output of fluid.

In recent years, since the application of clearance methods of determining renal blood flow and glomerular filtration rate, the kidney has been assigned a primary role in the accumulation of edema. The renal retention of salt was ascribed by Stead, Warren and Merrill to the effects of diminished blood supply to the kidney from the failing heart.² This was designated "forward failure" to the kidney and was considered to be the primary factor in edema formation, in contrast to the factors

of backward pressure in the peripheral capillary or to the effect of venous pressure upon the kidney itself.

In 1942 the first extensive studies correlating cardiac output with changes in the renal circulation and venous pressure were made by Seymour, Pritchard, Longley and Hayman.³ They found reduction in renal blood flow and glomerular filtration rate with a lowered cardiac output. After cardiac compensation, with a rise in cardiac output, the renal blood flow increased more than the glomerular filtration rate. They attributed the renal circulatory pattern during failure to the effect of high venous pressure upon the kidney. Later in 1944 Merrill confirmed these findings but noted that the diminution in renal blood flow correlated well with the diminution in cardiac output but had no correlation with the height of venous pressure.⁴ Merrill concluded that increased venous pressure was not the cause of the decreased renal blood flow with a relatively high glomerular filtration rate, but that the renal circulatory pattern was the result of inadequate output of the failing heart, causing constriction of the efferent glomerular arterioles which would tend to maintain the intraglomerular pressure.

This pattern of the renal circulation in cardiac failure is now well established. There may be constriction of the afferent glomerular arteriole also but there is relatively more of the efferent component. It is apparent that reduced blood flow due to

^{*} From the Physiological Division, Department of Medicine, The Johns Hopkins Hospital and University, Baltimore, Md.

Experimental studies supported by a grant from the Life Insurance Medical Research Fund. Work done in collaboration with Drs. Albert A. Kattus, Bruce C. Sinclair-Smith, Abraham Genecin, John Sisson, Carlos Monge, Jacques Genest and John Franklin. Read before the Johns Hopkins Medical Society March 14, 1949.

constriction of the efferent arteriole of the glomerulus tends to maintain or increase the pressure in the glomerular capillaries even though it offers resistance to the total blood flow. That this type of adjustment in the intrarenal circulation might take place was suspected by Starling and has been described extensively by Homer Smith and other workers.

The question then arises, how does this circulatory pattern bring about the reduction in excretion of sodium and chloride which are the main constituents of edema fluid? Merrill and Stead, and lately Leiter and Mokotoff, have elaborated further upon the relationship of the circulation to sodium retention by the kidney.⁵ They believe that the primary cause of the renal retention of sodium is the diminished glomerular filtration rate. They reason that the decrease in the amount of fluid filtered by the glomeruli, and hence of sodium presented to the tubules, causes the low output in the urine. It was suggested by Merrill that when the glomerular filtration rate falls below a "critical level" of about 70 cc./min., retention of sodium is marked because almost all of the filtered sodium is reabsorbed by the tubules.

Thus it has been shown that the renal blood flow and glomerular filtration rate are reduced in cardiac failure and it has been postulated that the primary change in the kidney responsible for sodium retention is decrease in the glomerular filtration rate.

Our studies were made to describe the mechanism of salt retention by the kidney by correlating the changes in renal function with the clinical and metabolic condition of the patient, also to determine some of the factors causing salt retention by a study of the effect of stress and drugs upon the kidney in normal subjects and patients with cardiac failure. In the study of the correlation of renal function with the clinical and metabolic condition of the patient we have followed the principle of making intensive study of a few patients throughout the course of their failure rather than a few observations on many patients at different stages of failure. If the theory that dimin-

ished filtration rate causes salt retention is correct, one might expect some correlation between the over-all balance of sodium and the level of glomerular filtration rate. Another principle which we have followed is that of accurately determining the body balance of electrolytes since the kidney is primarily responsible for the maintenance of this balance. If some function of the kidney is to be held responsible for the amount of edema, it seems inescapable that accurate proof of gain or loss of the extracellular fluid ions, sodium and chloride, must simultaneously be provided. Furthermore, since we suspected that changes in the composition of tissue cells might result from congestive heart failure we have determined the metabolic balances of nitrogen and of the main intracellular cation, potassium.

The first patient studied was a thirty-seven year old colored woman with marked congestive failure secondary to rheumatic mitral and aortic valvular deformities. There was no clinical evidence of active rheumatic fever. When admitted to the hospital she was markedly orthopneic and dyspneic while at rest in bed; there was distention of the neck veins and peripheral edema.

Figure 1 shows weight (solid dots) and venous pressure (hollow dots) with the periodic determination of glomerular filtration rate (GFR), renal plasma flow (RPF) and the filtration fraction (FF) during the course of four months. Each point concerning renal function represents an average of from three to six determinations during two to three hours on that day. During the first forty days weight loss, fall in venous pressure and symptomatic improvement were associated with a rise in renal plasma flow and fall in filtration fraction to normal. There was no significant change in the glomerular filtration rate. Thereafter the patient was at home and the circulatory status deteriorated again. She returned to the dispensary and was observed again to exhibit increased weight and venous pressure with markedly reduced renal plasma

flow but with the same glomerular filtration rate.

The glomerular filtration rate was quite constant and within normal limits for this patient throughout the entire period of observation. Her normal glomerular filtra-

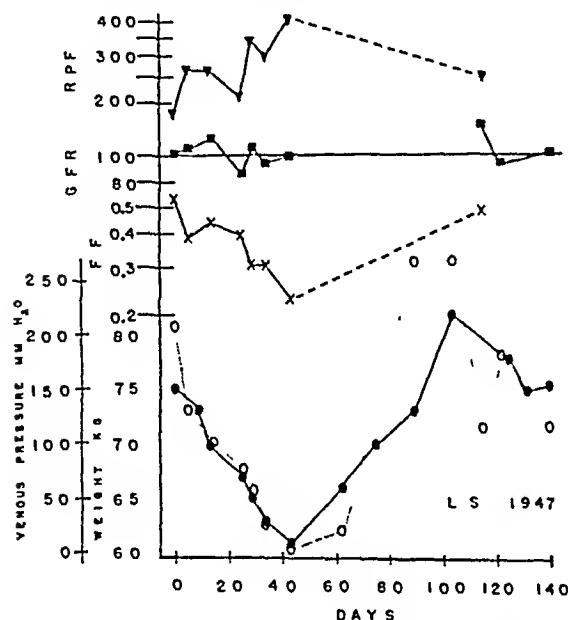


Fig. 1 Summary of the determinations of renal plasma flow (RPF), glomerular filtration rate (GFR), filtration fraction (FF), body weight (solid dots) and peripheral venous pressure (open circles) in patient L. S.

tion rate according to the standards of Homer Smith would be 100 cc./min. The range was 85 to 115 cc./min.

During the period of weight loss metabolic studies were performed on this patient. No medication except a maintenance dose of digitalis was given. (Fig. 2.) On the top of the chart are the periodic determinations of glomerular filtration rate (C_{in}), renal plasma flow (C_{PACA}) and filtration fraction (FF) over the twenty-four days of observation, with weight (WT) and venous pressure (VP). Below are the daily balance boxes for sodium, chloride, potassium and nitrogen determined by chemical analyses of the patient's dietary intake and urinary and stool output. The darkened areas when above the line represent negative balance or loss; when below the zero line, positive balance or retention. The distance from the bottom of the daily box up to the zero line represents the intake.

Loss of sodium and chloride were parallel to the drop in weight and venous pressure. At first the intake of sodium chloride was low (2 Gm. of sodium chloride); later the intake was raised by an additional 5 Gm. of sodium chloride. The increased intake had

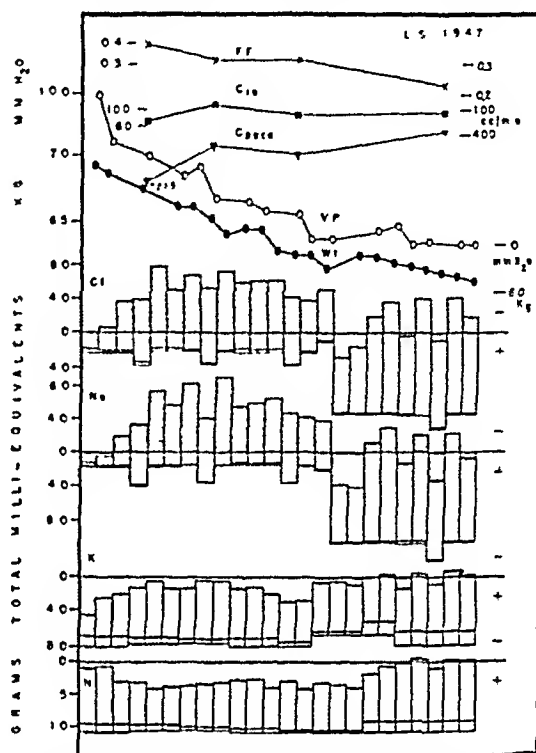


Fig. 2 The renal function determinations, venous pressure (VP), body weight (WT) and daily metabolic balance boxes for chloride, sodium, potassium and nitrogen in patient L. S. over the twenty-four days covering the period represented by days 20 to 44 in Figure 1. Nitrogen is in Grams, electrolytes in milli-equivalents. FF is filtration fraction, C_{in} is clearance of inulin or the glomerular filtration rate and C_{PACA} is clearance of para-acetyl-aminohippuric acid and is a measure of renal plasma flow. The shaded areas in the balance boxes when above the zero line represent negative balance or loss, and when below the zero line, positive balance or gain. The distance from the bottom of a box to the top is the total daily output and the distance from the bottom of the box to the zero line is the intake. The small section at the bottom of each box is the daily output in the stool. The remainder of the output is in the urine.

very little effect on the general course of sodium chloride balance, the kidney rapidly excreting the extra salt. All these changes in sodium and chloride balance and total output took place without any significant variation in the glomerular filtration rate.

We conclude from these observations during recovery from congestive failure that the excretion of sodium chloride is not necessarily correlated with changes in glomerular filtration rate. Furthermore, a normal glomerular filtration rate can be maintained during congestive failure.

Of interest is the marked change in the balances of potassium and nitrogen. Large amounts of nitrogen (representing 20 to 30 Gm. of protein a day) were retained for two weeks. Furthermore, the retention of potassium was more than could be accounted for on the basis of the ratio of the amount of potassium to nitrogen in body cells.⁶ There are two possible explanations for the protein storage. First, it may represent repletion of stores lost because of previous dietary inadequacy; second, it may represent repair of injury to body cells. Injury to cells might occur directly from circulatory insufficiency or by a catabolic reaction due to adrenal cortical activity. The retention of extra potassium might also be a replacement for sodium which had entered tissue cells during failure. These speculations concerning the significance of potassium and nitrogen retention obviously require further investigation.

The second patient was a thirty year old man with a history of rheumatic heart disease. He had dyspnea with minimal cyanosis on slight exertion. He had minimal but definite edema of the feet and a venous pressure of 160 mm. of water. His heart was enlarged to the left and right and the electrocardiogram revealed auricular fibrillation. Enlargement of the left auricle and calcification of the mitral valves were demonstrated by x-ray. He had been taking digitoxin, 0.1 mg. a day, for several months and this was continued with no other medication.

On the top of Figure 3, which covers one month, it is to be observed that the glomerular filtration rate was 70 to 80 cc./min., which is 50 per cent of the expected normal value for this patient since he was a large man. The renal plasma flow was 180 to 220 cc./min., which is about 30 per cent of

normal, resulting in an elevated filtration fraction of 0.40. Throughout the period of balance study no significant change in these values occurred. The initial loss of weight was accompanied by a fall in venous pressure from 160 mm. to normal and there

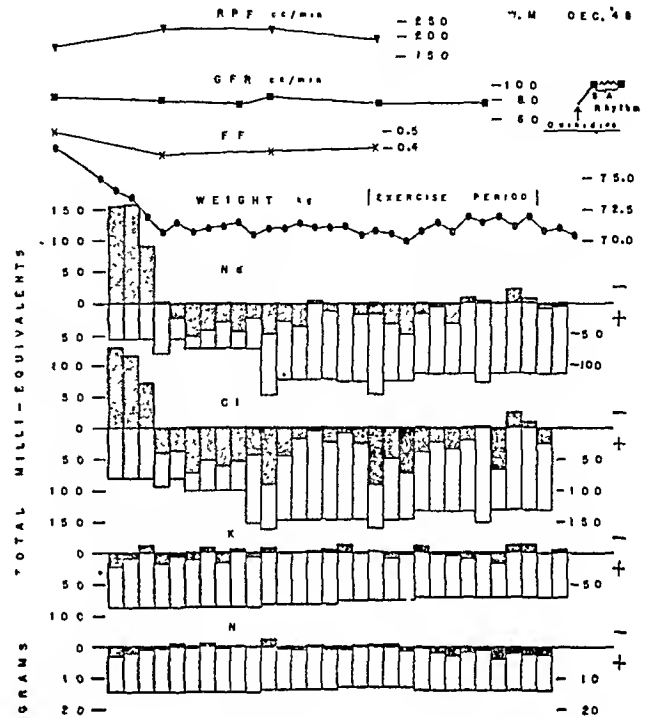


FIG. 3. The renal function determinations, body weight and daily metabolic balance boxes of sodium, chloride, potassium and nitrogen in patient W. M. After the metabolic studies were completed the patient's auricular fibrillation was converted to sinus rhythm by quinidine administration. This was followed by a rise in glomerular filtration rate to 100 cc./min., accompanied by no further weight loss. Method of construction of the balance chart same as in Figure 2.

was marked negative balance of sodium and chloride. Following this there was retention of sodium and chloride for several days. The total amount retained during this period was nearly equal to that lost previously. However, no change in weight accompanied this retention. During this phase the intake was changed from 3 Gm. of sodium chloride to 7 Gm. The extra salt was promptly excreted with no alteration in the balance pattern. Later the patient was allowed up and given daily exercise which was associated with some further sodium chloride retention. No significant gain or loss of potassium or nitrogen occurred in this patient.

We conclude from this study that a glomerular filtration rate 50 per cent of normal and a renal plasma flow diminished to one-third normal did not prevent loss of edema and superfluous body sodium, nor was there any correlation between either glomerular filtration rate or renal plasma flow and sodium chloride balance. This patient had persistent renal ischemia throughout the observation period and was able to excrete stored body sodium as well as sodium added to his intake. The renal blood flow did not increase with compensation as in the first patient.

It is of some incidental interest that after completion of the balance study the auricular fibrillation was converted to regular sinus rhythm by quinidine administration. This was accompanied by a definite rise in glomerular filtration rate which was probably a reflection of a more efficient cardiac mechanism producing increased output.

This patient showed no disturbance in potassium or nitrogen balance. It is difficult at this stage of our knowledge to speculate on the reasons for the difference between the behavior of potassium and nitrogen in the two patients. The latter patient had only mild congestion and edema and at no time was in as severe congestive failure as was the first patient. Another feature which is difficult to explain is the lack of weight gain associated with a significantly large retention of sodium and chloride. One wonders if a shift in body water occurred so that a loss in cell water balanced a gain in extracellular water. In other words, might there be a shift of water from cells to extracellular fluid which would require a gain in sodium and chloride without over-all gain in weight?

In general, from these case studies and others not reported here, we have found no simple correlation between the course of body sodium chloride balance and the renal circulatory pattern during recovery from congestive cardiac failure and edema. It is apparent that other factors must play a decisive role in governing the excretion of salt by the kidney. The idea that a diminution in glomerular filtration rate is the

primary reason for retention overlooks the possibility of metabolic or humoral influences upon the renal tubular cells which are responsible for the reabsorption of most of the glomerular filtrate. These metabolic changes might be initiated by the effects of inadequate circulation to other parts of the body. It is certainly not unreasonable to suspect that antidiuretic and salt-retaining humoral substances may be liberated and increase the renal tubular reabsorption of salt. Furthermore, very little or nothing is known about the influence of the renal nerves upon renal cell activity although nerve endings around the renal tubules were demonstrated by Berkley in 1893.⁷ Marshall demonstrated increased excretion of water and chloride by the denervated kidneys of dogs.⁸ These experiments have recently been repeated by Kriss, Fitcher and Goldman.⁹ I know of no proof of the nervous control of renal electrolyte excretion since the advent of modern methods for studying renal function.

Thus the renal tubular cells are exposed to many possible influences besides alterations in the amount of glomerular filtrate presented to them. Reduction in the amount of glomerular filtrate presented to the renal tubules may occur in cardiac failure but apparently other factors governing renal tubular activity are as important. The renal tubular cells are ultimately responsible for the regulation of output by selective reabsorption, allowing a small percentage of the filtered substances to escape into the urine.

Before concluding, one type of experiment should be considered which demonstrates a specific influence of exercise on sodium and chloride excretion and may represent in part the renal mechanism responsible for the edema in cardiac failure. The most common stress in our daily lives is exercise, standing and walking. In a patient with congestive failure it is known from clinical observation that ordinary daily exercise may lead to edema. The effect of mild exercise on normal people and on patients with cardiac failure has been investigated in

order to gain some insight into alterations in the renal mechanism which may occur.

The data in Figure 4 represent the effect of walking the length of the ward corridor ten times (200 yards) in thirty minutes on the renal circulation and electrolyte excretion in a patient with congestive cardiac failure. The patient was a fifty year old man who was admitted to the ward with congestive failure following an episode of substernal pain six weeks previously. He showed dyspnea on exertion, elevated venous pressure, an enlarged heart with normal rhythm and normal blood pressure. There was marked edema of the legs and some over the sacrum. The electrocardiogram was interpreted as showing evidence of an old anterior myocardial infarction. As seen on the lower portion of the illustration the glomerular filtration rate (C_{in} and C_{Cr}) was 80–90 cc./min. or about two-thirds normal, the renal plasma flow (C_{PACA}) 200 cc./min. or one-third normal with a filtration fraction of 0.3 to 0.4. There was no consistent change in filtration rate or renal plasma flow during the exercise. The pattern was that of renal ischemia with evidence of efferent glomerular arteriolar constriction producing a high filtration fraction. Above are the curves for the excretion of water and the electrolytes, potassium, phosphate, sodium and chloride. Since one is particularly interested in the reaction of the renal tubular cells to the glomerular filtrate, the urinary output of these substances has been expressed as the per cent of the glomerular filtrate which is excreted. In other words, a fall in the percentage excreted means that the tubular cells have reabsorbed a higher fraction of the amount of the substance presented to them by the glomeruli. Furthermore, the chart is so constructed that one can immediately detect a selective change in one electrolyte with respect to another. If the tubules are changing their percentage reabsorption in an unselective manner, the lines would all be parallel. Deviation of one line from another represents a selective

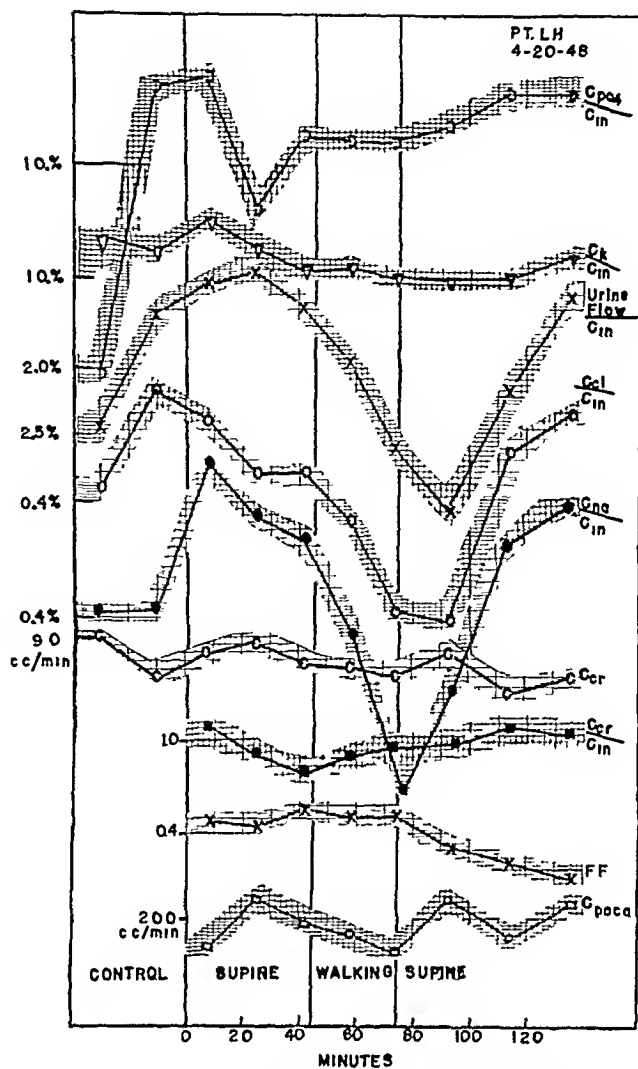


FIG. 4. The changes in renal function and electrolyte excretion during and following the injection of test materials (called "control" and first "supine" rest periods), during exercise (walking) and during a recovery rest period (second "supine" period). C_{PO_4} is plasma clearance of phosphate; C_K is clearance of potassium; CCl is clearance of chloride; C_{Na} is clearance of sodium; C_{Cr} is clearance of creatinine; FF is filtration fraction; C_{paca} is clearance of para-acetyl-aminohippuric acid and is a measure of renal plasma flow. Glomerular filtration rate was determined by both the clearance of inulin (C_{in}) and creatinine. The patient L. H. had congestive cardiac failure with edema at the time of observations. In this patient specific sodium and chloride retention occurred without significant changes in the glomerular filtration rate or renal plasma flow measurements. The excretion of potassium and phosphate was unaffected by the exercise and did not parallel the marked fall in sodium and chloride excretion. This pattern of electrolyte excretion is typical of that seen in the patient with cardiac failure. Frequently a fall in glomerular filtration rate is observed also. This type of response to exercise can be observed in normal subjects, with or without a measurable drop in glomerular filtration rate. In the cardiac subject the retention of sodium chloride is much more marked than would be observed generally with the same amount of mild exercise in a normal subject.

change in exact proportion to the relative distances between the lines on the chart.

It is apparent that a dramatic selective change in the excretion of sodium, chloride and water occurred without significant change in potassium, phosphate or the glomerular filtration rate during exercise. The change in sodium is ten-fold, and return to the pre-exercise values occurs after rest.

The investigator must be careful in this type of experiment to observe the effects of the injected substances on renal function. During the period marked "control" are recorded the changes in electrolyte excretion caused by the injection during the first ten minutes of the test substances, inulin and para-acetylaminohippuric acid. These changes are recorded in order to be certain that a fairly steady state is reached before exercise is begun. It is known from other experiments that the electrolyte excretions would be parallel and nearly constant if no exercise were performed after these adjustments took place. These observations serve to emphasize that the interpretation of electrolyte excretion patterns must be made with the closest scrutiny of the test conditions and the effect of substances injected.

It is concluded, then, that inadequate output of the failing heart may produce complicated and profound metabolic effects on peripheral tissues as well as on the functions of the kidney. The patient must be studied not only at rest but also under the stresses of daily activity. Only then can one obtain an integrated picture of the many inter-related factors involved in the production and retrogression of congestion and edema. It has been noted that ischemia of the kidney occurs presumably as a result of inadequate cardiac output. This may cause some retention of sodium and chloride by diminishing glomerular filtration rate. However, the ultimate responsibility for retention rests with the specific selective mechanisms of the renal tubular cells whose reabsorptive activity must be sensitive to factors other than the reduction in the amount of fluid presented to them by the diminished circulation. The effects of pos-

ture, exercise, humoral substances and the renal nerves have yet to be adequately determined, and the nature of the metabolic injury to other tissues is a relatively unexplored phase of the problem.

Many people have contributed to this work which began with a study of methods of determining renal function with Dr. James Bordley III and Dr. Louis Alpert in 1942. In carrying out the metabolic balance studies we have had the advice and cooperation of Dr. John Eager Howard and the technical assistance of Mr. Harry Eisenberg and Miss Dorothy Wagner. The dietary regulation and calculations were carried out by Miss Janette Carlsen, Mrs. Lucille Opie and Mrs. Barbara Crozier. The chief contribution of work in the laboratory has been made by Miss Marion Birmingham and Miss Margot Robinson. We have also had the advice of Drs. E. K. Marshall, Kenneth Blanchard and E. Cowles Andrus.

REFERENCES

1. SPARRING, E. H. *Fluids of Body*. Herter Lecture, New York, 1909. W. T. Keener and Co.
2. WARRIN, J. V. and STRAD, E. Fluid dynamics in chronic congestive heart failure, interpretation of mechanism producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure. *Arch Int Med*, 73 138, 1944.
3. STAMOUR, W. B., FRITCHARD, W. H., LONGLEY, L. and HAYMAN, J. M. Cardiac output, blood and interstitial fluid volumes, total circulating protein and kidney function during cardiac failure and after improvement. *J Clin. Investigation*, 21 229, 1942.
4. MERRILL, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure, evidence of "forward failure" as the primary cause. *J Clin Investigation*, 25 389, 1946.
5. MOKOTOFF, R., ROSS, G. and LEITER, L. Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. *J Clin Investigation*, 27 1, 1948.
6. REIFENSTEIN, E. C., JR., ALBRIGHT, F. and WELLS, S. L. The accumulation, interpretation and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus and nitrogen. *J Endocrinol*, 5 367, 1945.
7. BRIDLEY, H. J. The intrinsic nerves of the kidney. A histological study. *Bull Johns Hopkins Hosp*, 4 1 1893.
8. MARSHALL, E. K. and KOLLS, A. C. Studies on the nervous control of the kidney in relation to diuresis and urinary control. *Am J Physiol*, 49 302, 1919.
9. KRISS, J. P., FUTCHER, P. H. and GOLDMAN, M. L. Unilateral adrenalectomy, unilateral splanchnic nerve resection and homolateral renal function. *Am J Physiol*, 154 220, 1948.

Tricuspid Stenosis—A Simple Diagnostic Sign^{*}

HARRY VESELL, M.D.

New York, New York

FOR a long time the occurrence of tricuspid valvular disease had been considered rare and its clinical recognition almost impossible. Studies¹⁻⁸ during the past ten years, however, have added much to our knowledge of this valvular lesion. It has been shown that the condition is not so rare and that its clinical diagnosis can often be made. Nevertheless the definitive diagnosis of a tricuspid lesion, and specifically of tricuspid stenosis, is still difficult at the bedside. The following observations are recorded to describe a new clinical sign which is simple to elicit and indicative if not pathognomonic of tricuspid stenosis.

CASE REPORT

P. S., a forty-four year old white man, dress operator, was admitted to the medical service of Beth Israel Hospital. There was no history of polyarthritis or chorea but he was known to have had a cardiac condition for twenty-five years. This was asymptomatic for twenty-two years during which time he worked regularly. During the three and a half years prior to admission he attended the cardiac clinic of the hospital because of dyspnea, orthopnea and slight cough, some lack of his usual endurance and weakness. He also had been having attacks of precordial distress, sensations of internal pressure of moderate severity, lasting ten to twenty minutes each two to five times a week; these were not especially related to exertion but caused him to stop work temporarily. For two to three months before admission these symptoms grew worse and he had frequent attacks of paroxysmal nocturnal dyspnea. His sputum was often blood-tinged.

Physical examination revealed him to be well

developed and well nourished, slightly dyspneic and slightly cyanotic. His temperature was normal. The sclerae were not icteric. The heart percussed enlarged to the left and downward. The apical impulse was felt 12 cm. from the midline in the fifth intercostal space. A systolic thrill was felt over the base especially over the aortic area. The following murmurs were heard: at the apex a loud, rough systolic and a less rough diastolic and presystolic; at the base a loud, rough systolic and a faint, blowing, early diastolic, loudest over the aortic area; at the tricuspid area (just to the right of the lower sternum) a rough, moderately loud diastolic murmur; a thrill was not felt over this area. A_2 equalled P_2 and was not accentuated. The rate was 80 to 90 per minute and regular. The radial pulses were small. The blood pressure was 135/90. With the patient in the sitting position the neck veins were distended and were seen to have fairly marked pulsations. When these pulsations, felt over the right carotid and jugular area, were correlated with the heart sounds they did not seem to be systolic in time. With the index finger of the left hand placed over the right jugular pulse near the base of the neck and the index finger of the right hand placed in the suprasternal notch, the impulses felt under both hands were quite forceful but not synchronous; the jugular came just before the one in the suprasternal notch. The latter was systolic and due to the pulsation of the dilated aorta and innominate artery; the former, venous and presystolic, apparently was produced by the contracting hypertrophied right atrium.

Over the lung bases, right and left, a few rales were heard on inspiration. The respiratory rate was 32 per minute. The liver was enlarged to three fingerbreadths below the costal margin and gave an impulse synchronous with the heart beat. The spleen was not palpable. There

^{*} From the Medical Service of Beth Israel Hospital, New York, N. Y.

was slight pretibial edema; no clubbing was present.

Laboratory data were as follows: The urine showed 1+ albumin. The hemoglobin was 15.0 Gm. (per cent); erythrocytes 5,630,000 per c.mm. of blood. The blood Wassermann test was negative. The erythrocyte sedimentation rate was 5 mm. in forty-five minutes. N.P.N. of the blood was 39 mg. per cent. The venous pressure was equal to 17 cm. of water. The patient was not cooperative enough accurately to record the circulation time.

The teleroentgenogram revealed the cardiac silhouette to be markedly enlarged and fluoroscopy disclosed enlargement of all chambers, dilatation of the aorta and calcification of the aortic valve. The electrocardiogram was typical of the pattern associated with left ventricular strain.

The diagnosis was rheumatic heart disease, enlarged heart, mitral stenosis, mitral insufficiency, aortic stenosis, aortic insufficiency and tricuspid stenosis; regular sinus rhythm and class iv (classification of New York Heart Association).

There was considerable improvement in response to cardiac therapy but after ten days he insisted on leaving the hospital. One month later he was readmitted and stated he had been confined to bed at home most of that month and had taken his medication, 0.2 Gm. digitalis, daily. However, the dyspnea, orthopnea and weakness increased. There were occasional chest pains as before. His physician finally advised him to return to the hospital. This time he appeared very tired, dyspneic and slightly orthopneic. There was some cyanosis of the face and nail beds. Jaundice was not present. The physical findings were about the same as recorded one month before on the previous admission. There were more rales at both lung bases.

The neck veins were distended and pulsations were visible. The strong presystolic pulsation felt in the jugular area was again noted to "saw-saw" with the systolic impulse felt in the supra-sternal notch. The enlarged liver and its pulsations were felt. The diastolic murmur was again heard to the right of the lower sternum. Icterus index was 10. The electrocardiogram revealed no significant changes from the one previously described. Because of a rise in temperature to 101°F. on the second day a blood culture was taken but found sterile. The patient this time

failed to respond to therapy; symptoms increased and rales at the lung bases became more numerous. The temperature rose to 103°F. on the fourth day and the patient succumbed on the next, the fifth day of the second admission, apparently of cardiac failure and possible hypostatic pneumonia or pulmonary infarction.

Postmortem examination was performed by Dr. Henry Brody. The veins in the neck were unusually distended, sufficiently so on the left to make prominent one of the valves in the external jugular vein. The pericardial sac was markedly distended, containing 300 cc. of clear, light yellow fluid. The pericardial surfaces were smooth and glistening. The heart weighed 800 Gm.; it was roughly quadrilateral, measuring 16 by 16 cm. The anterior surface was made up almost equally by the right and left ventricles. The tips of the auricular appendages, both right and left, also appeared in the anterior view. The right atrium showed marked roughening and thickening of its epicardial surface. The diameter was but slightly increased; the trabecular markings were very prominent. A very small organized thrombus was present in the tip of the auricular appendage. The tricuspid valve was partly stenosed, not admitting two fingers. It was roughly elliptical, the axes measuring 2 and 1 cm., respectively. There was complete fusion of the valves at the commissures so that the individual cusps could not be distinctly recognized. The valve was thickened, irregularly nodular and somewhat stiffened. The chordae tendinae were only slightly thickened. They did not appear shortened. The right ventricle was small. The columnae carnae appeared moderately rounded. The chamber was filled with a large amount of postmortem clot.

From the ventricular aspect the thickening and deformity of the line of closure of the tricuspid valve were quite prominent. The right ventricular myocardium measured 5 mm. in thickness in the region of the outflow tract. The circumference of the pulmonic valve was 6 cm. The posterior cusp in its left half was folded so that the normal free edge was adherent to the pulmonic surface of the valve. The new edge so formed was thick and showed a number of pinhead, glistening, grayish-white nodules. There was some thickening of the adjacent left cusp. The pulmonary artery showed only small, early atheromatous plaques. The left atrium was slightly dilated, its wall rather markedly thick-

ened. The foramen ovale was closed. The left auricular appendage was negative. There was some ridging and wrinkling of the atrial endocardium posteriorly. The mitral valve was narrowed, forming a somewhat curved slit slightly less than 3 cm. in length. Its ring was completely calcified, forming knobby protrusions into the lumen. On the endocardium were seen a number of smaller than pinhead, glistening nodules.

The left ventricle showed some degree of dilatation. The columnae carnae were definitely flattened. There was very marked hypertrophy of the wall, reaching a thickness of 18 mm. From the ventricular surface the marked stenosis and insufficiency of the valve was very striking. The chordae tendineae were markedly thickened but appeared stretched rather than flattened. A small moderator band was present, extending from the anterior surface to the mid-portion of the interventricular septum. There was marked graying and thickening of the endocardium of the interventricular septum immediately below the aortic valve. The aortic valve could best be viewed from above. The size of the lumen was entirely fixed due to calcification of the valve cusps. The lumen was almost circular with an approximate diameter of 11 mm. The cusps and their commissures were markedly thickened, calcified and showed many calcific protruberances. The calcification along two of the commissures extended up the aorta for a distance of less than 1.5 cm. The wider of the two was 1.4 cm. Above these the ascending portion of the aorta was relatively free of any change except for a band of yellow atheroma-like deposit, 1 cm. wide and 5 cm. in length. There was also an area about 1 cm. in diameter which showed small, glistening, reddish elevations. The coronary orifices were not involved in the calcific process. The coronary arteries in their first portions were markedly sclerotic and in places calcified. There was, however, no serious impairment of the lumen at any point, and no ulcerations or thrombi.

In the lungs there were a few, small, fresh hemorrhagic infarcts at both bases; the pulmonary arteries showed practically no atherosclerotic change. There were 100 cc. of light orange, clear fluid in the right pleural cavity and less than 200 cc. in the left.

The liver weighed 1,180 Gm.; it measured 22 by 18 by 7 cm. Its markings were somewhat accentuated; lobulations were distinct.

Microscopically, sections of the heart showed no evidence of active rheumatic inflammation. Perivascular, mostly acellular scars were numerous. The endocardium showed fibrous thickening; the muscle fibers showed hypertrophy. Sections of lung, liver, spleen and kidney showed chronic passive congestion.

COMMENT

Venous phenomena are usually mentioned in descriptions of tricuspid valvular disease. The veins of the body are engorged and dilated and the pressure therein increased. The veins in the neck are of particular concern. The prominent "a" wave in the jugular sphygmogram has been frequently referred to, as has the presystolic impulse in the veins of the neck and in the liver. The marked and chronic systolic pulsations of the deep jugular veins, a "vigorous pulsation raising the sternocleidomastoid," has been emphasized by White and Cook^{3,6} although they also indicated the absence of notable pulsation in the neck veins and liver in some cases.

Mackenzie⁹ told of one case in which a large wave was sent back from the hypertrophied auricle with such force that it caused the valves in the jugular and subclavian veins to close with a snap which he heard over these veins as a clear, sharp sound preceding the first heart sound.

Some believed that without knowing the time of the pulse waves in the neck (or liver), the clinical diagnosis of tricuspid stenosis was not warranted. Wolferth⁸ emphasized that the characteristic impulse in the veins in the neck in tricuspid stenosis should be presystolic. Crighton Bramwell has indicated the diagnostic value in tricuspid stenosis of a powerful auricular impulse which he recorded in the jugular sphygmogram.¹⁰ With auricular fibrillation the presystolic impulse is lost, and in nodal rhythm its timing is different.

In our case, demonstrated at necropsy to have tricuspid stenosis, a marked presystolic impulse was felt over the right jugular vein just above the clavicle and over the sternocleidomastoid muscle. This



FIG. 1. Position of hands to elicit impulses over the jugular vein and episternal notch

was of surprising force for a venous pulse. It was easily timed by comparison with the systolic aortic impulse in the episternal notch palpated by the index finger of the other hand. (Fig. 1.) A see-saw movement was conveyed to the two palpating fingers by the two vascular pulsations. The strong presystolic venous impulse over the jugular vein was considered caused by the contraction of the hypertrophied right atrium; this impulse was well transmitted to the neck because of the obstruction at the stenotic tricuspid orifice causing a damming-back action, the right atrium being unable to empty itself readily. Transmission of the impulse was also aided by the increased venous distention and increased pressure in

the large veins central to this area. We have never felt a presystolic impulse in the jugular vein in congestive heart failure without tricuspid stenosis. The systolic impulse in the episternal notch due to the pulsation of the adjacent dilated aorta and innominate artery was undoubtedly modified by the aortic valvular disease present. It is increased by the insufficiency of the valve though decreased by the stenosis, lesions which accompany most cases of tricuspid stenosis.

SUMMARY

A simple sign characteristic of tricuspid stenosis is described. A case of tricuspid stenosis with necropsy findings is reported in which this sign led to the correct ante-mortem diagnosis.

REFERENCES

1. ALTSCHULT, M. D. and BUDNITZ, E. Rheumatic disease of the tricuspid valve. *Arch. Path.*, 30: 7, 1940.
2. ALTSCHULT, M. D. and BLUMGART, H. L. The circulatory dynamics in tricuspid stenosis. *Am. Heart J.*, 13: 589, 1937.
3. COOK, T. and WHITE, P. D. Tricuspid stenosis—with particular reference to diagnosis and prognosis. *Brit. Heart J.*, 3: 147, 1941.
4. DRESSER, W. *Clinical Cardiology*. New York and London, 1942. Paul B. Hoeber.
5. FRILDIANDER, R. D., and KERR, W. J. The clinical diagnosis of tricuspid stenosis. *Am. Heart J.*, 11: 357, 1936.
6. GARVIN, C. F. Tricuspid stenosis—incidence and diagnosis. *Arch. Int. Med.*, 70: 104, 1943.
7. SMITH, J. A. and LEVINE, S. A. The clinical features of tricuspid stenosis. *Am. Heart J.*, 23: 739, 1942.
8. WHITE, P. D. and COOK, W. T. The recognition and significance of marked and chronic systolic pulsation of the deep jugular veins. *Tr. A. Am. Physicians*, 54: 199, 1939.
9. MACKENZIE, SIR JAMES. *Diseases of the Heart*. 3rd ed., p. 337. London, 1921. Henry Frowde and Hodder and Stoughton.
10. BRAMWELL, C. and KING, F. *The Principles and Practice of Cardiology*. P. 151. London, 1942. Oxford University Press.

Diaphragmatic Hiatus Hernia*

With Severe Iron-deficient Anemia

STEVEN O. SCHWARTZ, M.D. and SUNOLL A. BLUMENTHAL, M.D.

Chicago, Illinois

THAT diaphragmatic hiatus hernia is not a rare anatomic variation, as earlier medical literature seemed to indicate, is now well established. Improved methods of diagnosis and increased awareness of the condition have brought it to the foreground during the past several years. Giffin¹⁵ in 1912 was able to collect a total of only 650 proved cases from the literature of which but fifteen were diagnosed during life, and Pancoast and Boles²⁸ were able to find only thirty-two additional cases so diagnosed prior to 1923. These figures contrast strikingly with more recent reports. Harrington¹⁸ found that at the Mayo Clinic alone 600 cases of diaphragmatic hernia were diagnosed between 1926 and 1941. According to Murphy and Hay²⁵ the incidence of hiatus hernia in gastrointestinal x-ray studies done by various authors has varied from 0.75 to 2.9 per cent. Mendelsohn²³ found sixteen cases in 1,000 consecutive gastrointestinal studies for an incidence of 1.6 per cent, while Schatzki³⁰ reported an incidence of 3.5 per cent in 1,500 gastrointestinal roentgen examinations.

The esophageal hiatus type is the most common form of diaphragmatic hernia. Of the 295 cases that Harrington¹⁸ treated surgically, 223 were at the esophageal hiatus. The remainder occurred in the following order: left hemidiaphragm forty-one, short esophagus type fourteen, hiatus pleura peritonealis seven, absent posterior fourth of the left diaphragm five, foramen Morgagni four, right hemidiaphragm one. The

stomach was the only organ involved in 231 of these cases, and participated with various other organs of the peritoneal cavity in an additional fifty-five cases, being involved in 286 out of 295 cases.

Diaphragmatic hernia typically occurs in the short, stocky, middle-aged, multiparous female. The symptoms are so variable that the condition may masquerade as almost any disease of the upper abdomen or chest. Most common diagnostic errors in order of frequency, according to Harrington,¹⁸ were cholecystitis, cholelithiasis, gastric ulcers, duodenal ulcers, hyperacidity, secondary anemia, cardiac disease, cancer of the cardia, stricture of the esophagus, appendicitis and intestinal obstruction. There are certain clinical manifestations, however, which should enable the clinician to diagnose or, at least suspect, the presence of a hiatus hernia in some instances. The more common abdominal symptoms^{1,16,19,26} in order of frequency are epigastric pain, a feeling of distress during or after meals and associated with bloating, belching, heart burn, nausea, vomiting and regurgitation, night pain or pain in the recumbent position, dysphagia and hiccough. Hiatus hernia has often been confused with anginal symptoms and coronary artery disease^{11,12,20,21} because of the presence of substernal pain with occasional radiation of the pain to the left arm.

Definitive diagnosis of diaphragmatic hernia is, of course, made on the basis of x-ray findings. The diagnosis of the larger

* From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Ill. Aided by a grant from the Wilson Laboratories, Chicago, Illinois.

hernias, with all or a good portion of the stomach in the thoracic cavity, is very easy roentgenologically. The smaller or reducible hernias are likely to escape discovery unless the examiner is alert for clues that will stimulate careful study. Such clues, according to Harrington,¹⁷ are (1) displacement of the lower segment of the esophagus, (2) a tortuous but not dilated terminal esophageal segment, (3) angulated segment, (4) undue retardation of the barium stream at the hiatus, (5) level of gastric contents above the esophageal aperture, (6) what apparently is high hour-glass contraction of the stomach with a visible niche at the site of constriction is, in fact, often a hernia of the stomach through the diaphragm with the ulcer merely a complication.

In spite of the increasing frequency with which hiatus hernia is recognized, sufficient emphasis has not been placed on its ability to produce a profound anemia.

There are many reports describing gastric ulcers in the herniated portion of the stomach. Bright⁵ is credited with the first description in 1836. Carman and Fineman⁶ in 1924 were probably the first roentgenologists to mention bleeding and anemia which occurred in three of their twenty cases diagnosed by x-ray. Öhnell²⁷ in 1926 was the first to point out the correlation between hiatus hernia and bleeding. Boek,³ in a discussion of one of the Cabot cases in 1929, emphasized the relationship between gastrointestinal hemorrhage and hiatus hernia. He cited three cases in which occult blood was found in the stools and an anemia was present. The only abnormal roentgenologic findings were those of hiatus hernias. In 1933 Gardner¹⁴ reviewed the English literature on anemia associated with hiatus hernia. He was able to collect twenty-two previously published cases including those reported by Segal,³³ Mathews and MacFee²² Weitzen³⁷ and Truesdale.³⁵ To these he added six unpublished cases making a total of twenty-eight. Of these seventeen were females and eleven males. Nineteen patients were over forty years old and fourteen had demonstrable loss of blood. Boek, Dulin and

Brooke⁴ in 1933 reported a series of ten patients. They emphasized the "silent" nature of this condition, the absence of physical signs and the tendency to recurrent bleeding. In their series there were nine females and one male, their ages ranging from fifty-one to seventy-nine years. Moersch²⁴ noted the presence of gastrointestinal bleeding with weakness and evidence of anemia in thirty-two of the 246 patients with hiatus hernia encountered at the Mayo Clinic from 1932 to 1937. In this series there were 133 females and 113 males. The average age was fifty-five, the youngest eight and the oldest eighty-two. Cowan's⁹ observations were based on forty-five cases studied from 1930 to 1935 at Mount Sinai Hospital, New York. He had thirteen cases in the "severe secondary anemia" group. His comments regarding these are pertinent: "In the anemia group the presenting symptoms are those usually associated with severe anemias such as weakness, anorexia, dyspnea and pallor. Very few if any gastric symptoms are in association with the anemia. The case histories of all these patients show the presence of a long-standing secondary anemia with evidence of bleeding from the gastrointestinal tract *not due* to ulcers, varices, or any other organic disease."

Murphy and Hay²⁵ in 1943 reported on seventy-two patients with hiatus hernia at the Peter Bent Brigham Hospital. There were sixty-one women and eleven men. The average age was sixty, the youngest thirty-three and the oldest seventy-eight. Hemoglobin values were available for sixty-seven of the patients and of these twenty-three had levels below 10 Gm.

Among other clinicians who have commented on the relationship of anemia to hiatus hernia are Schiro and Benjamin,³¹ Sahler and Hampton,²⁹ Ohler and Ritvo,²⁶ Weinberg,³⁶ Mendelsohn,²³ Dyke and Dyas,¹⁰ Trueman³⁴ and Andrews.¹

Bleeding has even been observed in infants. Christiansen⁸ in 1937 reported a case of hiatus hernia associated with hematemesis in a one year old child. Bergenfeldt⁷ reported a case of hematemesis in an eight-

een month old boy in whom there was cessation of bleeding after repair of the hiatus hernia.

The anemia accompanying hiatus hernia is due to any or all of the following causes: (1) passive congestion, (2) ulcer due either to varicosities resulting from passive congestion or a disturbed blood supply and (3) inflammation in the region of the wall of the viscera incarcerated in the hiatus of the hernia. Boch et al.⁴ demonstrated by operative and postmortem examination that in the great majority of their cases the cause of bleeding was due to simple congestion of the mucous membrane and some enlargement of the veins in the walls of the herniated portion of the stomach. The mucosa in the non-herniated portion appeared normal. Gastric ulcers occurring in the herniated portion of the stomach have been reported by Mathews and MacFee,²² Truesdale,³⁵ Feldman¹³ and Harrington.¹⁷ Harrington states that "the ulcer is due to trauma and is usually situated in the lower end of the esophagus close to its juncture with the stomach and it may be found in that portion of the stomach in the hernial sac near the lesser curvature. These traumatic ulcers result from the to and fro action of the stomach in the hernial ring when the hernia is small as well as from the forceful pressure exerted on the large distorted and congested stomach during the attacks of vomiting when the hernia is large. There is also the additional factor of regurgitation of gastric juices into the lower part of the esophagus which produces esophagitis . . . After repair of the hernia and replacement of the stomach into its normal position most of these traumatic ulcerations heal spontaneously." Commenting on the type of bleeding from these traumatic erosions he states that they may be severe, and hematemesis or melena is often one of the chief signs. In other instances the patient may not be aware of any blood loss and yet have a very marked anemia resulting from occult bleeding. This type occurred in 11 per cent of his series.

Chevallier and Danel⁷ suggest that the

anemia is caused by a torpid inflammatory process in the affected region of the gastric wall.

CASE REPORTS

CASE I. S. F., a sixty-one year old white female, complained of pain in the legs, especially at night; palpitation and "nervousness" for several years; occasional episodes of "heart-burn"; precordial pain with radiation down the left arm, not related to exertion but relieved by sodium bicarbonate. Her menopause occurred at the age of fifty-four with no subsequent bleeding. Diagnosis of esophageal hiatus hernia was made at the age of fifty-seven. At that time her blood count was as follows: hemoglobin 50 per cent, red blood cells 4.00, white blood cells 9,600, differential within normal limits. X-ray showed an unusually large cardio-esophageal hiatus hernia, the size of a lemon, projecting above the diaphragm into the retrocardiac space, with the esophagus invaginating into the hernia. The rest of the gastrointestinal tract was normal on x-ray examination. Arthritic changes were noted in the lower cervical intervertebral spaces and also in the lumbar spine. Stool examinations were consistently negative for occult blood.

She was first seen by the senior author at the age of fifty-nine. The symptoms had not significantly changed. Physical examination revealed a very pale, obese white female. Except for a soft systolic murmur over the pulmonic area the remainder of the examination was essentially negative. Her hemoglobin now was 33 per cent (5.1 Gm.), red blood cells 4.08, white blood cells 12,700, hypochromia 3+, anisocytosis 4+, polychromatophilia 1+, poikilocytosis 4+. The differential count was: polymorphonuclears 64 per cent, lymphocytes 24 per cent, monocytes 10 per cent, basophils 1 per cent, eosinophils 1 per cent. The presence of the hiatus hernia was confirmed. (Fig. 1.) She was given ferrous sulfate and improved satisfactorily hematologically. About a year later, following intermittent iron therapy, she had 83 per cent (12.9 Gm.) hemoglobin and 4.44 red blood cells. Stools were intermittently positive for occult blood. When last seen she had a hemoglobin of 92 per cent (14.4 Gm.) and red blood cells 5.11.

CASE II. H. S., a fifty-three year old white female, complained chiefly of dyspnea on the slightest exertion for two months; hair quite dry, nails "break in layers" for months; and

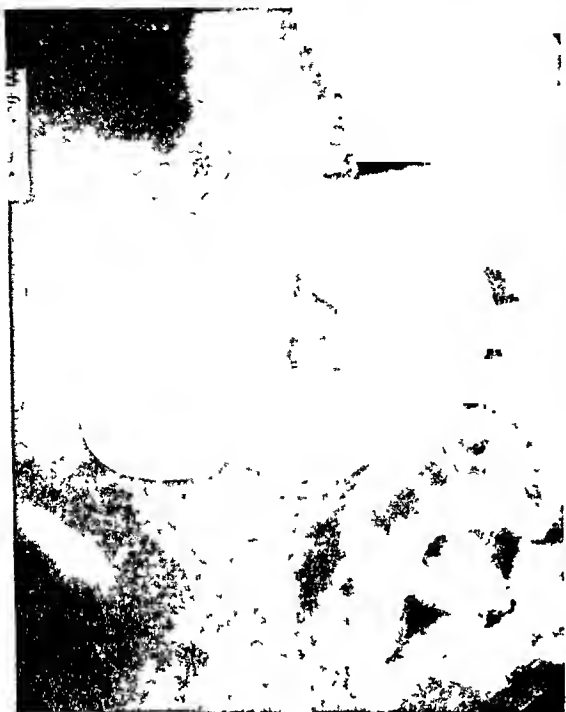


FIG. 1. Large cardio-esophageal hiatus hernia, Case 1.

numbness in the fingers especially during the mornings. Her past history revealed that she had an induced menopause eight years previously, hypertension for the last few years and an 80 per cent hemoglobin a year before. Her diet had been adequate and there had been no known source of bleeding. Positive physical findings were the pallor, an uncoated tongue with a moderate atrophy of the papillae and the fragile but not very thin nails. Blood findings were: hemoglobin 41 per cent (6.5 Gm.), red blood cells 3.21, white blood cells 6,250, microcytosis, anisocytosis, poikilocytosis and hypochromia were moderate, platelets were increased; polymorphonuclears 60 per cent, lymphocytes 26 per cent, monocytes 7 per cent, eosinophils 6 per cent, basophils 1 per cent. Roentgenologic examination of the gastrointestinal tract was negative except for a "large hiatus hernia of the stomach. The portion of the stomach in the hernia showed coarse mucosal folds and there was a spot in the front showing conversion of the mucosal folds which is suspected to be an ulcer crater." The patient has done well clinically on ferrotherapy.

CASE III. T. J., an eighty-three year old, white female, complained chiefly of easy fatigability. She was under treatment for hypertensive heart disease for several years. Physical



FIG. 2 Large hiatus hernia, Case III.

examination revealed a rather pale, obese, white female. Except for the enlarged left heart and the elevated blood pressure nothing remarkable was found. Blood findings were: hemoglobin 40 per cent (6.3 Gm.), red blood cells 2.50, white blood cells 7,500, platelets adequate, polymorphonuclears 58 per cent, lymphocytes 38 per cent, monocytes 4 per cent, anisocytosis 2+, poikilocytosis 2+ and hypochromia 2+.

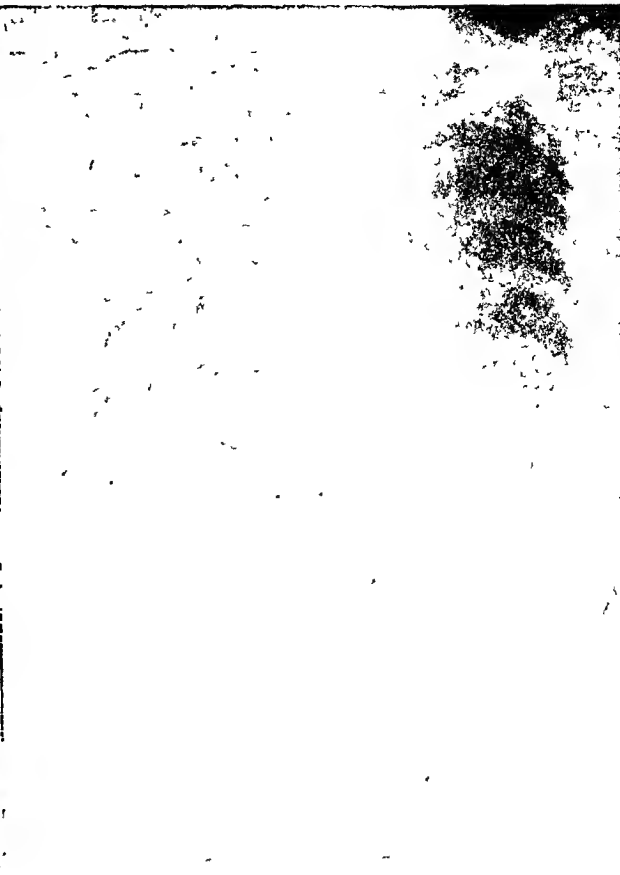
Roentgenologic examination of the gastrointestinal tract disclosed a large hiatus hernia of the stomach with a small diverticulum at the greater curvature side of the herniated portion of the stomach. (Fig. 2.) No intrinsic lesion was noted in the stomach or the duodenum. The patient was given iron therapy and showed a gratifying clinical and hematologic response.

CASE IV. A seventy-seven year old white female, complained of palpitation, shortness of breath and tiredness. For six months she had been in bed most of the time. She was found to have severe anemia four years previously when, at the time of her pneumonia, she had three blood transfusions. Eighteen months before she was hospitalized for a rectal abscess and again had two transfusions because of anemia. A blood count at that time showed the following: hemoglobin 19 per cent (2.9 Gm.), red blood cells 2.49, white blood cells 11,450, polymorphonuclears 77 per cent, lymphocytes 16 per cent,



3

FIG. 3. Large hiatus hernia, Case iv.



4

FIG. 4. Elevation of right diaphragm which was interpreted as "an unusual domed separate diaphragmatic leaf." This patient had the large diaphragmatic hernia shown in Figure 3.

monocytes 7 per cent, hypochromia 4+, anisocytosis 4+, poikilocytosis 2+. She was given weekly "shots" after being discharged from the hospital and took eight Lextron capsules a day for a few months. Physical examination revealed an obese, pale, white female. A blowing systolic murmur was present at the mitral and aortic areas. The nails were soft and the hair was dry and moderately coarse. The remainder of the physical examination was negative. Blood count at this time revealed hemoglobin 56 per cent, (8.7 Gm.), red blood cells 3.39, white blood cells 11,800, platelets increased, polymorphonuclears 78 per cent, lymphocytes 15 per cent, eosinophils 2 per cent, monocytes 5 per cent, hypochromia 2+, microcytosis 2+.

Chest x-rays at the time of the pneumonia revealed in addition to the pulmonary consolidation "a radiolucent shadow with a horizontal fluid level lying just behind the apex of the heart and which probably represents a diaphragmatic hernia with a fluid level." (Figs. 3 and 4.) This was subsequently confirmed by barium meal. The patient was again given iron therapy and has done well since.

CASE V. L. C., a seventy-seven year old white female, experienced a sudden onset of weakness, malaise, anorexia and continuous borborygmi ten days prior to her admission. The following day she noted tarry stools. After that she remained weak and tired, had marked nausea, pain in the right upper quadrant and swelling of the upper abdomen. Twenty years before she had "yellow jaundice" which disappeared spontaneously and for eighteen years she received therapy for a very "bad liver." Selective dyspepsia to sauerkraut, fried foods, etc., was noted by the patient. She was found to be very pale and obese. Her blood pressure was 180/70. An occasional inspiratory wheeze was heard in the bases posteriorly. The heart was moderately enlarged to the left; a soft systolic murmur was heard at the apex and a blowing systolic murmur at the aortic area. There was some tenderness in both the right and left upper quadrants. Examination of the blood revealed hemoglobin 27 per cent (4.4 Gm.), red blood cells 2.06, white blood cells 7,300. The stools were positive for occult blood. X-ray examination disclosed a diaphragmatic hernia with the cardiac portion



FIG. 5. Large diaphragmatic hernia, Case v.

of the stomach through the hiatus. No ulcerations or varicosities could be detected in the herniated portion of the stomach. (Fig. 5.)

She received four transfusions of blood and iron therapy. Improvement, however, was slow due to continuation of gastrointestinal bleeding.

CASE VI. C. N. B., a seventy-six year old white female, complained of increasing weakness, dyspnea on exertion of six months' duration and arthritis involving the lower dorsal vertebrae for ten years. There was no weight loss and no known blood loss. She was obese and very pale. Her blood pressure was 160/75. The remainder of the examination was not significant. Blood findings were: hemoglobin 31 per cent (4.8 Gm.), red blood cells 2.59, white blood cells 5,700, hypochromia 4+, anisocytosis 4+, poikilocytosis 1+, polychromatophilia 2+. Stools contained from a trace to 4+ occult blood. Roentgenologic examination revealed an esophagus foreshortened into a large hiatal hernia, the size of an orange.

There was a dramatic clinical and hematologic response to iron therapy.

CASE VII. M. D., a white female, approximately fifty years of age, complained of fainting spells, described as "blackout sensations," which lasted about five to ten minutes and occurred daily during the week before admission to the

hospital. She also experienced dyspnea, palpitation on exertion and weakness during this period. No previous history was significant. Physical examination showed a moderately enlarged left heart with a systolic murmur in the mitral region. Blood findings were: hemoglobin 36 per cent (5.6 Gm.), red blood cells 3.43, white blood cells 10,300 with an essentially normal differential count. The red cell showed marked microcytosis and hypochromia. X-rays revealed that the barium passed to the lower third of the esophagus without hesitation. At this point the esophagus was tortuous and a diaphragmatic hernia was present. From this the barium passed freely into the stomach and filled it and the duodenal bulb without demonstrating further lesions. The patient discharged herself two weeks after admission but returned five days later because of a recurrence of the fainting spells. At this time her hemoglobin was 24 per cent and red blood count 2.24. She remained in the hospital for another week and again was discharged "against advice." Her further course is unknown.

CASE VIII. D. M., a sixty-four year old white female, complained of swelling of the legs, weakness, palpitation, pounding in the head, tiredness, numbness of the fingers and gastrointestinal upsets of two to three weeks' duration. The physical examination was non-contributory. Blood examination revealed: red blood cells 3.3, hemoglobin 30 per cent (4.7 Gm.), white blood cells 6,000, differential within normal limits, except for the red cells which showed marked microcytosis and hypochromia. X-ray revealed a hiatus hernia the size of an apple. The esophagus was normal in length and entered the diaphragmatic hernia posteriorly. Stools were positive for occult blood. The patient was given iron therapy and a bland diet on which she improved. Blood findings eight months later were: hemoglobin 12.5 Gm. and red blood cells 4.3.

CASE IX. B. A., a forty-one year old white male, complained chiefly of "fainting spells." The first episode occurred two years before admission, there being two the first year, three the second year and two the preceding month. The fainting spells were usually accompanied by profuse sweating and dizziness. He had lost 10 pounds in the last three months. There was no known history of bleeding. Physical examination revealed nothing of significance. He was obese and very pale; blood pressure was 130/80.

The blood findings were: red blood cells 3.23, hemoglobin 34 per cent (5.3 Gm.), white blood cells 8,500, polymorphonuclears 75, lymphocytes 15, monocytes 10. The red cells on smears were very small and hypochromic. Stools contained 2+ blood on repeated examinations.

temesis fifteen years previously following a strenuous lecture tour. Some epigastric "burning" relieved by alkali on several occasions during the past year was admitted. Physical examination revealed nothing extraordinary excepting the marked pallor. Blood examination revealed

TABLE I
SUMMARY OF CASES I TO X

No.	Name	Age	Sex	Lowest Known			Symptoms			X-ray Findings
				RBC	Hgb. %	Color Index	Gastro-intestinal	Cardio-vascular	Other	
I	S. F.	61	F	4.1	5.1 Gm. 33	.40	+	+	+	Large cardio-esophageal hiatus hernia
II	H. S.	53	F	3.2	6.4 Gm. 41	.68	0	+	+	Large hiatus hernia with suspicious ulcer crater
III	T. J.	83	F	2.5	6.3 Gm. 40	.80	0	+	+	Large hiatus hernia with a small diverticulum
IV	G. S.	77	F	2.5	2.9 Gm. 19	.38	0	+	+	Large diaphragmatic hernia
V	L. C.	77	F	2.1	4.4 Gm. 27	.64	+	0	+	Diaphragmatic hernia with herniation of cardiac portion of stomach; acute gastrointestinal hemorrhage the presenting symptom
VI	C. V. B.	76	F	2.6	4.8 Gm. 31	.60	0	+	+	Foreshortened esophagus with large hiatus hernia
VII	M. D.	50+	F	2.2	3.7 Gm. 24	.55	0	+	+	Diaphragmatic hernia
VIII	D. M.	64	F	3.3	4.7 Gm. 30	.45	+	+	+	Diaphragmatic hernia with normal esophagus entering the hernia posteriorly
IX	B. A.	41	M	3.2	5.3 Gm. 34	.53	0	0	+	Diaphragmatic hernia with normal esophagus; inconstant herniation of stomach into chest cavity
X	J. W.	52	M	2.0	4.4 Gm. 28	.70	+	0	+	Large para-esophageal diaphragmatic hernia

Roentgenologic examination disclosed that in the upright position the distal end of the esophagus was displaced to the right in the lateral view by what was interpreted as being stomach lying inferior to the diaphragm. In the Trendelenburg position a considerable portion of the stomach was seen to pass above the diaphragm into the chest and to lie superimposed on the spine and slightly to the right of it.

CASE X. J. W., a fifty-two year old white male, complained of weakness so marked that he could not stand long enough to finish shaving. He slept eighteen to twenty-two hours a day. The onset was gradual over a period of years but fairly more marked over the past two months. There was a vague history of hema-

red blood cells 2.0, hemoglobin 28 per cent, white blood cells 6,000, differential within normal limits, and increase in platelets; hematocrit was 16 per cent. The stools were positive for occult blood. X-ray of the stomach revealed a large para-esophageal diaphragmatic hernia in which no ulcer was demonstrable. Following 1,500 cc. of whole blood, a bland diet and ferrotherapy the patient was remarkably improved and has continued well to the present time.

COMMENT

The analysis of our cases merely re-emphasizes the presence of certain charac-

teristic features associated with gastric hiatus hernia. It is known to be a condition most commonly found past middle age, predominantly in short, stocky, obese females. Our patients averaged about sixty-three years and with three exceptions were over 50. Twelve of the twenty were females.

Physical examination revealed nothing extraordinary except marked pallor and obesity. This absence of physical findings, evidence of weight loss, masses, tenderness or resistance in the abdomen became important clues in the recognition of the cases clinically in the last group of cases.

TABLE II
SUMMARY OF CASES XI TO XX

No	Name	Age	Sex	Lowest Known			Symptoms			X-Ray Findings	Remarks
				RBC	Hgb %	Color Index	Gastro-intestinal	Cardio-vascular	Other		
xi	W S	40	M	2 15	4 7 Gm 30	69	+	+	0	Diaphragmatic hernia	Tarry stools
xii	B R	48	F	2 82	4 8 Gm 31	55	+	0	+	Large hiatus hernia	
xiii	L M	53	F	3 30	5 3 Gm 34	51	+	+	+	Diaphragmatic hernia of cardia	Autopsy proved
xiv	J D	65	M	3 36	6 7 Gm 43	64	+	0	0	Small diaphragmatic hernia	Hematemeses, hernia surgically repaired and a shortened esophagus was found
xv	E B	66	M	1 68	2 2 Gm 14	42	0	0	+	Diaphragmatic hernia	
xvi	S S	69	M	2 50	6 5 Gm 42	84	+	0	+	Diaphragmatic hernia	Tarry stools
xvii	A H	71	F	2 45	3 9 Gm 25	51	+	+	+	Diaphragmatic hernia with large ulcer crater in herniated portion of stomach	
xviii	J D	72	M	2 79	3 9 Gm 25	44	+	+	+	Large hiatus hernia involving cardia of stomach	"Bloody stools"
xix	F G	72	F	2 40	6 7 Gm 43	89	0	+	+	Small hiatus hernia	"Bright red blood in stool", x-ray examination of gastrointestinal tract (except hernia) negative, proctoscopy negative
xx	D M	81	M	2 97	7 3 Gm 47	78	+	0	+	Diaphragmatic hernia	Tarry stools

Their general appearance fitted well the accepted prototype. (Tables I and II.)

Interesting in the histories was the paucity of gastrointestinal symptoms. Twelve patients had complaints referable to the abdomen but these were seldom marked. Cardiovascular symptoms were much more prominent, being present in all but eight patients. Their nature was variable and had its genesis partly in the anemia and partly in the degenerative changes present incidental to the advanced age. The other symptoms were divisible into those related to the hiatus hernia and consequent anemia and those simply co-existing. Among the former might be mentioned weakness, dryness of the hair, splitting of the nails and coldness and numbness, while among the latter were "nervousness," arthritic pains and selective dyspepsia.

Our attention was focused on the remarkable anemia present in every instance, which indirectly was responsible for the patient consulting a physician and which in turn gave an early clue to the nature of the disability. In this connection the red blood cell count is of relatively little value, as we have pointed out previously,³² except that it aids in the determination of the color index. The physiologic severity of the anemia is indicated by the hemoglobin level which varied from 2.2 to 7.3 Gm. (14 to 47 per cent). The fact that all these patients were ambulatory, indicating a gradual adjustment to the low hemoglobin, and that the color index in most cases was very low, signifies that the bleeding was of a duration long enough not only to have depleted the body's iron stores but also to have dissipated a goodly portion of the circulat-

ing hemoglobin. In all instances in which the color index was greater than 0.7 (except Case III) recent acute blood loss, as manifested by tarry stools or hematemesis, complicated the chronic bleeding.

In only two cases was an ulcer crater seen. The bleeding is apparently quite irregular and unpredictable. The same patients, under what appeared to be the same conditions, showed anywhere from none to 4+ occult blood. Since all patients were thoroughly studied for other gastrointestinal bleeding lesions and none were found, and since most have been followed for a time sufficient to have revealed an early or small bleeding neoplasm, it may be assumed that the bleeding actually was from the herniated portion of the stomach. This is further borne out by the frequency with which blood was found in the gastric contents when examined. The response to iron therapy was gratifying as was expected since we were dealing with a relatively pure iron deficiency and since the rate of loss was far less than regenerative capacity.

SUMMARY

Twenty patients with diaphragmatic hiatus hernia were studied. Bleeding from the stomach in these patients resulted in severe iron-deficient anemias. There was a paucity of symptoms directing attention to the gastrointestinal tract but cardiovascular symptoms were quite prominent. Physical findings were negligible.

In a patient, especially a female past middle age, who presents an iron-deficient type of anemia without a history of bleeding, localizing symptoms and physical findings of significance, a diaphragmatic hiatus hernia should be suspected and ruled out.

The authors wish to acknowledge with gratitude the kindness of Drs. M. D. Allweis, H. Arkin, Wm. Boikan, A. U. Derman, S. L. Goldberg, J. Waller and S. Weisberg who permitted their cases to be included in the present series.

REFERENCES

1. ANDREWS, K. S. Diaphragmatic hernia. *Am. J. Digest. Dis.*, 2: 310, 1935.
2. BERGENFELDT, E. Ein Beitrag zur Kenntnis des Zwerchfellbruches. *Acta chir. Scandinav.*, 83: 519, 1940.
3. BOCK, A. V. Treatment in an obscure case (Cabot case 15022). *New England J. Med.*, 200: 88, 1929.
4. BOCK, A. V., DULIN, J. W. and BROOKE, P. A. Diaphragmatic hernia and secondary anemia; 10 cases. *New England J. Med.*, 209: 615, 1933.
5. BRIGHT, R. Account of a remarkable missplacement of the stomach. *Guy's Hosp. Rep.*, 1: 598, 1836.
6. CARMAN, R. D. and FINEMAN, S. Roentgenologic diagnosis of diaphragmatic hernia. *Radiology*, 3: 26, 1924.
7. CHEVALIER, P. and DANIEL. Anémie chlorotique et hernie diaphragmatique chez une femme âgée. *Sang*, 16: 67, 1944.
8. CHRISTIANSEN, H. A case of hematemesis in an infant due to esophageal orifice hernia. *Acta radiol.*, 18: 77, 1937.
9. COWAN, I. I. Diaphragmatic hiatus hernia. *Am. J. Roentgenol.*, 37: 333, 1937.
10. DYKE, S. D. and DYAS, G. E. Herniation of stomach with anemia. *Lancet*, 1: 119, 1940.
11. ERNSTENE, A. C. Differential diagnosis of coronary artery disease. *J. Kansas M. Soc.*, 36: 441, 1935.
12. ERNSTENE, A. C. and MCGURL, F. J. Esophageal hiatus hernia associated with hypochromic anemia and angina pectoris; report of case. *Cleveland Clin. Quart.*, 7: 209, 1940.
13. FELDMAN, M. Peptic ulcer of lower esophagus associated with esophageal hiatus hernia; report of 2 cases. *Am. J. M. Sc.*, 198: 165, 1939.
14. GARDNER, K. D. Diaphragmatic hernia associated with secondary anemia. *Am. J. M. Sc.*, 185: 561, 1933.
15. GIFFIN, H. Z. The diagnosis of diaphragmatic hernia. *Ann. Surg.*, 55: 388, 1912.
16. HARRINGTON, S. W. Diaphragmatic hernia; symptoms and surgical treatment in 60 cases. *J. A. M. A.*, 101: 987, 1933.
17. HARRINGTON, S. W. Diagnosis and treatment of various types of diaphragmatic hernia. *Am. J. Surg.*, 50: 381, 1940.
18. HARRINGTON, S. W. Roentgenologic considerations in diagnosis and treatment of diaphragmatic hernia. *Am. J. Roentgenol.*, 49: 185, 1943.
19. HEDBLUM, C. A. Diaphragmatic hernia; study of 378 cases in which operation was performed. *J. A. M. A.*, 85: 947, 1925.
20. HERRICK, J. B. On mistaking other diseases for coronary thrombosis. *J. M. Soc. New Jersey*, 32: 590, 1935.
21. LINTZ, W. New conception of diaphragmatic hernia. *M. Rec.*, 159: 25, 93, 1946.
22. MATHEWS, F. S. and MACFEE, W. F. Gastric ulcers dependent upon diaphragmatic hernia. *Ann. Surg.*, 94: 517, 1931.
23. MENDELSON, E. A. Hiatus hernia of stomach as source of gastro-intestinal bleeding. *Radiology*, 46: 502, 1946.
24. MOERSCH, H. J. Hiatal hernia. *Ann. Otol., Rhin. & Laryng.*, 47: 754, 1938.
25. MURPHY, W. P. and HAY, W. E. Symptoms and incidence of anemia in hernia of esophageal hiatus. *Arch. Int. Med.*, 72: 58, 1943.
26. OHLER, W. R. and RITVO, M. Diaphragmatic

- (hiatus) hernia; clinical study. *New England J. Med.*, 229: 191, 1943.
27. ÖHNELL, H. Diaphragmatic hernia of esophageal hiatus from clinical view point. *Acta radiol.*, 6: 23, 1926.
 28. PANCOAST, H. K. and BOLES, R. S. Nontraumatic left diaphragmatic hernia; clinical and roentgenologic studies in 15 cases. *Arch. Int. Med.*, 38: 633, 1926.
 29. SAHLER, O. D. and HAMPTON, A. O. Bleeding in hiatus hernia. *Am. J. Roentgenol.*, 49: 433, 1943.
 30. SCHATZKI, R. Hiatus hernia. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 45: 177, 1932.
 31. SCHIRO, H. S. and BENJAMIN, J. E. Severe anemia associated with diaphragmatic hernia. *Ohio State M. J.*, 36: 164, 1940.
 32. SCHWARTZ, S. O. and FLOWERS, V. C. Morphologic changes in red blood cell with iron deficiency anemia. *J. A. M. A.*, 130: 622, 1946.
 33. SEGAL, H. L. Secondary anemia associated with diaphragmatic hernia. *New York State J. Med.*, 31: 692, 1931.
 34. TRUEMAN, K. R. Diagnosis and treatment of para-esophageal hiatus hernia. *Canad. M. A. J.*, 56: 149, 1947.
 35. TRUESDALE, P. E. Gastric ulcer associated with diaphragmatic hernia. *New England J. Med.*, 207: 385, 1932.
 36. WEINBERG, J. Diaphragmatic hernia; collective review. *Internat. Abstr. Surg.*, 72: 445, 1941.
 37. WEITZEN, M. Diaphragmatic hernia with severe anemia. *Am. J. Roentgenol.*, 28: 808, 1932.

Biologic Complications of Penicillin Therapy*

LEONARD S. SOMMER, M.D. and CUTTING B. FAVOUR, M.D.

New York, New York

Boston, Massachusetts

NOT long after the introduction of sulfonamide compounds a variety of untoward reactions was encountered. Like other drugs with a relatively low therapeutic index these reactions took the form of drug fevers, rashes, hematologic and urologic complications and, in large measure, have been responsible for some caution in their general use. In a broad sense a more interesting complication of sulfonamide medication has been the development during the past decade of drug resistance by some strains of bacteria, notably the gonococcus. Since the sulfonamides have not been as powerful antibacterial agents as penicillin, this ecologic rumbling has only suggested the violent shifts in host-parasite relationships which may follow the use of drugs with extremely high therapeutic indices. Like the sulfonamides, penicillin also is a double-edged weapon against disease.

In the doses we use the common allergic drug reactions are not encountered unless the drug is taken locally or orally. In certain other situations, however, indirect reactions of a biologic nature, depending upon the alterations in bacterial flora, are now being seen. For example, vitamin deficiencies may be induced by changing the bowel flora,¹ resistant strains of bacteria may replace the organisms found in the respiratory and genito-urinary tract²⁻⁵ and finally strains of bacteria normally absent or present in small numbers may cause acute illness⁶⁻⁸ or even death. The purpose of this paper is to cite examples of this latter type of complication following penicillin therapy. Although these are single examples and repre-

sent an unusual therapeutic difficulty, they emphasize the importance of using penicillin with the same careful clinical indications with which we apply other, less spectacular remedies.

CASE REPORTS

CASE I. M. D. (No. 81365), a sixty-eight year old white female, entered the hospital on August 27, 1946, because of persistent vomiting, periumbilical pain and weight loss of three weeks' duration. A posterior gastro-enterostomy had been performed in 1931 for a poorly controlled gastric ulcer. She had been well until postprandial epigastric pain recurred in 1945, at which time a gastrojejunal ulcer was demonstrated by x-ray. Three weeks before admission weight loss, anorexia, pain and vomiting recurred. The remainder of the past history was non-contributory.

Physical examination revealed a poorly nourished elderly woman complaining of abdominal discomfort. Temperature was 98°F. (54.4°C.), pulse 112, respirations 22 and blood pressure 120/75 mm. Hg. The chest was moderately emphysematous and hyper-resonant to percussion. Examination of the lungs and heart was otherwise unremarkable. The abdomen showed only direct periumbilical tenderness. The remainder of the examination was negative.

The blood Hinton test was negative. Examination of the urine and the stool guaiac test were negative. On admission hemoglobin was 11 Gm. per cent, hematocrit 34 per cent, white blood cell count 8,500 with a normal differential. Blood chemical values were not remarkable. A gastrointestinal series revealed a jejunal ulcer. Electrocardiogram showed premature auricular contractions.

On a Sippy II diet, high protein drinks and intravenous fluids the patient improved but symptoms persisted and the nightly gastric

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.

residue was 500 cc. On the sixteenth hospital day prophylactic penicillin, 40,000 units every four hours intramuscularly, was started and a subtotal gastric resection with a Polya type anastomosis was performed. The immediate postoperative course was satisfactory. On the second postoperative day the patient's temperature rose to 103°F. and the patient became cyanotic. The trachea and heart were shifted to the left and there was dullness at the left base. The white cell count was 1,150 per cu. mm. with 32 per cent polymorphonuclear leukocytes. An electrocardiogram showed sinus tachycardia. In spite of oxygen, morphine, heparin and penicillin the patient remained in semi-shock for twelve hours and then expired.

Postmortem examination performed three hours after death revealed a confluent bronchopneumonia of the lower two-thirds of the left lung with a small left hydrothorax. The lung had the consistency of soft liver. Five microscopic sections showed an acute cellular reaction and many bacilli, both free and within phagocytes. Multiple cultures of the involved pulmonary tissue yielded a pure growth of *Bacterium coli*. No other pathologic cause for death was found.

Comment. An elderly woman with pulmonary emphysema who was treated with prophylactic penicillin therapy in the course of a gastric resection for intractable ulcer symptoms developed an overwhelming bronchopneumonia and died two days postoperatively. Postmortem examination revealed as the cause of death an extensive bronchopneumonia due to *Bact. coli*.

CASE 11. H. K. (No. 82287), a sixty-seven year old white male, was admitted to the hospital on December 14, 1946, with a diagnosis of carcinoma of the stomach. During the previous eight months the patient had had continuous epigastric pain associated with anorexia, constipation and a weight loss of 30 pounds. The diagnosis of gastric cancer had been made but because of an unexplained anemia and leukopenia operation had been delayed. Three days before admission the patient became completely obstructed. The past history was non-contributory.

On entry the temperature was 99.4°F. (44.2°C.), pulse 90, respirations 20 and blood pressure 112/55 mm. Hg. The patient was an emaciated, chronically ill, dehydrated elderly man. A few rales were heard at the left base

of the lung. The heart was slightly enlarged to the left. The abdomen gave a sensation of fullness in the epigastrium but no mass was felt. The rectum contained impacted feces. The remainder of the examination was not significant.

The blood Hinton test was negative. Urine showed 1+ protein and 5 to 10 white blood cells per high power field. Hemoglobin was 10.2 Gm. per cent, white blood cell count 1,800 with 20 per cent neutrophils and 80 per cent lymphocytes. Blood urea nitrogen was 26 mg. per cent and the serum total protein 5.7 Gm. per cent.

The patient was placed on intermittent Wangenstein suction, high protein drinks and was given parenteral fluid and vitamin therapy. With prophylactic sulfadiazine, 2.5 Gm. daily, and penicillin, 50,000 units intramuscularly every three hours beginning immediately before operation, a subtotal gastrectomy was performed on the fifth hospital day and the tumor was removed from its adherence to the pancreas. The early postoperative course was uneventful but the next day the patient had a shaking chill and the temperature rose to 104°F. There were numerous moist rales in both lungs and a chest x-ray was consistent with a widespread peribronchial pneumonia which was more widespread on the right than on the left. The white blood cell count was 1,900 per cu. mm. The urine was clear. Sulfadiazine was discontinued and penicillin was increased to 50,000 units every two hours. At no time did the patient vomit. His condition deteriorated in spite of oxygen and blood transfusions. Shock supervened and the patient expired on the eighth hospital day.

At the autopsy performed four and one-half hours postmortem the cause of death was found to be marked bronchopneumonia involving all lobes of both lungs; it was interpreted as resulting from aspirated material. Four stained microscopic sections showed the alveoli to be filled with huge numbers of gram-positive and gram-negative bacteria, with a sparse cellular reaction. Three specimens of lung tissue grew *Proteus vulgaris* in pure culture and a fourth, *Pseudomonas aeruginosa*. There was no evidence of metastatic disease and the operative site was intact.

Comment. An emaciated elderly man with adenocarcinoma of the stomach had a gastric resection with prophylactic penicillin therapy. Postoperatively the patient de-

veloped fatal bronchopneumonia which failed to respond to larger doses of penicillin. Autopsy revealed extensive pneumonia due to *P. vulgaris*.

CASE III. C. P. (No. G5420) (Figs. 1 to 2B) a sixty-nine year old, white, retired toolkeeper was

men was doughy and peristaltic sounds were markedly diminished. The liver and spleen were not felt. There was no clubbing or edema of the extremities.

The blood Hinton test was negative. The white blood cell count was 15,900 per cu. mm. with 96 per cent neutrophils and the hemato-

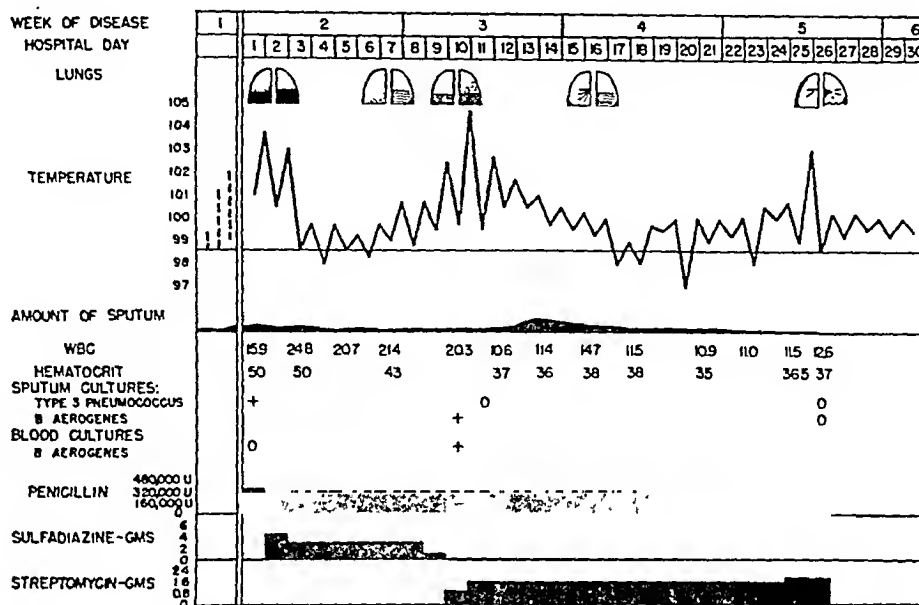


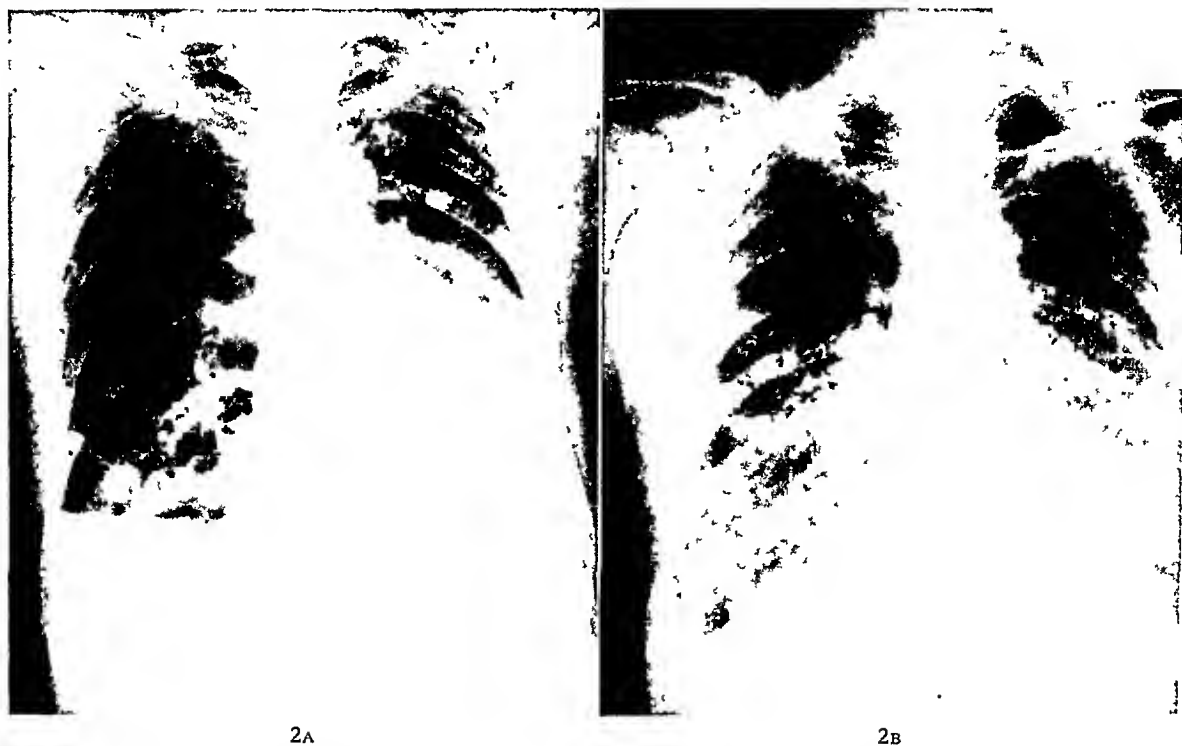
FIG. 1. Hospital course of Case III (C. P. Medical No. G5420). Note the gradual elevation in temperature to a high spike with chill on the tenth hospital day, concomitant with the recovery of pure cultures of *B. aerogenes* in sputum and blood.

admitted to the hospital on October 19, 1947, because of fever, cough and dyspnea. During the previous ten years the patient had had a chronic productive cough without hemoptysis and had had four bouts of bronchopneumonia. He had drunk alcohol heavily for years. For three years he had been maintained on digitalis with fair cardiac compensation. For two years the patient had not been working. Six days before admission he noted an increase in his cough. On the day before admission he developed a fever of 102°F. and became delirious.

Physical examination on admission revealed an acutely ill, moderately well oriented man, dyspneic, slightly cyanotic and dehydrated. The temperature was 103°F. (57.2°C.) by rectum, pulse 126 and regular, respirations 36 and blood pressure 140/70 mm. Hg. The tongue was coated and the pharynx reddened. The trachea was in the midline. The chest was emphysematous; there was decreased expansion of the left lung with dullness, bronchovesicular breath sounds and sticky inspiratory rales over the right middle and both lower lobes of the lungs. The heart showed sinus tachycardia which was confirmed by electrocardiography. The abdo-

crit was 50 per cent on admission. The urine contained 2+ protein and 6 to 10 white blood cells and occasional granular casts per high power field. Blood urea nitrogen was 68 mg. per cent. The sputum was green and tenacious, not copious in amount, and yielded in almost pure culture *Pneumococcus* type III, with rare alpha and beta hemolytic streptococci. Blood culture was negative. X-ray of the chest showed mottled areas of consolidation in the lower half of each lung field. (Fig. 2A.)

The patient was placed in an oxygen tent, given intravenous glucose solution and intramuscular penicillin 120,000 units immediately and 40,000 units every three hours thereafter. This was supplemented for seven days with sulfadiazine 0.5 Gm. every four hours and sulfamerazine 0.5 Gm. every eight hours by mouth. He was maintained on digitalis 0.1 Gm. daily. The patient's temperature was normal by the third hospital day (Fig. 1), but on the seventh day spikes to 100.5°F. began to appear. On the tenth day the patient had a severe shaking chill and the temperature was found to be 104.5°F. and the white blood cell count 20,300 per cu. mm. Bronchial breath sounds



2A

2B

FIG. 2 A, Case III, chest film on admission to the hospital with pneumococcal pneumonia, B, chest film showing spread of pneumonic infiltration, especially in right lung field at the time of clinical relapse due to *B. aerogenes*

were heard throughout most of both lung fields (Fig. 2B.) Since this episode was thought to be due to a new invading organism, streptomycin 0.2 Gm every three hours was added to the penicillin injections. Cultures of the nose, throat and blood all yielded growth of *Bact. aerogenes*, the former two sources also containing small numbers of *Staphylococcus albus*. The patient's temperature dropped promptly and then slowly reached a normal level by the sixteenth day. The patient's subsequent course was long but uncomplicated. During this time his appetite and sense of well being improved, signs and x-ray evidence of pulmonary consolidation regressed and on the twenty-sixth day cultures of the throat grew only alpha streptococci. Follow-up films three months later still showed marked fibrosis at the site of his previous pneumonia.

Comment. An elderly man with emphysema, chronic bronchitis, probable bronchiectasis and a history of recurrent pulmonary infections of ten years' duration contracted pneumococcal pneumonia which responded clinically and bacteriologically to penicillin therapy. On the tenth day of penicillin treatment, however, he developed evidence of blood stream and pulmonary

re-infection due to *Bact. aerogenes*. A high index of suspicion and the prompt addition of streptomycin to the therapeutic regimen resulted in rapid regression of the pneumonic process and recovery from infection.

CASE IV R W (No. M6527), a twenty-two year old colored man was admitted to the hospital for the ninth time on March 5, 1948. The patient had been followed since childhood at the Children's Hospital and more recently at the Peter Bent Brigham Hospital for sickle-cell anemia. There had been multiple admissions for hemolytic crises. In 1941 the patient was hospitalized for a pneumococcus, type III pneumonia of the left lower lobe which was successfully treated with sulfathiazole. For four days before the present admission the patient had a sore throat with mild cough and on the day of entry he developed fever, some shortness of breath and pain in the left anterior chest.

Examination revealed a thin, acutely ill colored boy in moderate respiratory distress. The temperature was 102.4°F. (56.9°C), pulse 104, and blood pressure 118/64 mm Hg. There were many bronchial rales and slightly diminished breath sounds at the left base and axilla. The heart was enlarged with a rapid regular

rate and a grade II systolic apical murmur. The spleen was not palpable and the remainder of the examination was not remarkable.

The blood Hinton test was negative. The urine showed 1+ protein and occasional white blood cells. Hemoglobin was 10 Gm. per cent, hematocrit 30 per cent and the white blood cell count 26,000 with 88 per cent neutrophils and many sickle forms on smear. Except for a bilirubin of 5.0 mg. per cent blood chemical values were normal. Stool guaiac was negative. On admission a sputum culture yielded a heavy growth of *Diplococcus pneumoniae* with a few *Hemophilus influenzae* and *Neisseria catarrhalis*. X-ray of the chest revealed a triangular area of consolidation at the left base.

Within twelve hours after treatment with penicillin, 50,000 units intramuscularly every three hours, the temperature was normal. Within twenty-four hours, however, the patient had a chill and the temperature rose to 103.6°F. The white blood cell count was 28,000 per cu. mm. and physical and x-ray examination revealed a spread of the area of consolidation in the left lower lobe. An immediate gram-stained smear of the throat and sputum showed predominance of gram-negative rods. On culture these were identified as *H. influenzae*. A few colonies of beta hemolytic streptococci were also cultured. Streptomycin, 175 mg. every three hours, or 1.4 Gm. per day, was given in addition to penicillin therapy, and during the next five days the temperature gradually dropped to normal. Sputum culture on the eighth day grew no *H. influenzae*. After fifteen days of such combined chemotherapy the lungs cleared considerably and at the time of discharge on the twenty-second hospital day the patient was well.

Comment. A young colored man with long-standing sickle-cell anemia developed pneumonia with an initial sputum culture containing many pneumococci and a few *H. influenzae*. Following twelve hours of penicillin therapy the patient improved. On the second day, however, pneumonic infiltration extended, coincident with the appearance in the sputum of *H. influenzae* in large numbers. No pneumococci were recovered at this time. Streptomycin treatment was instituted at the time of clinical relapse on the basis of the gram-stained

smears of the throat and sputum which showed an abundance of small gram-negative rods. After discontinuation of combined therapy cultures no longer contained either *D. pneumoniae* or *H. influenzae*.

OBSERVATION

Four case histories are presented which demonstrate clearly the importance of following shifts in bacterial flora of certain patients during specific antibiotic therapy. Two of the patients came to autopsy and were found to have extensive bronchopneumonia due to gram-negative organisms. Each of them had received prophylactic and postoperative penicillin for gastrointestinal surgery. The third patient was first treated for pneumococcus pneumonia superimposed upon extensive chronic pulmonary disease. Penicillin therapy cleared the pneumococcus infection but was promptly followed by recurrence of pneumonia and septicemia due to *B. aerogenes*. This infection was brought under control by streptomycin. In the fourth patient pneumococcus pneumonia responded to penicillin but was followed by a relapse of pneumonia due to *H. influenzae*. The latter organism had been present in the initial cultures before penicillin therapy. The *H. influenzae* infection was successfully treated with streptomycin.

Each of these patients had underlying poor resistance to disease. The two surgical patients were complicated problems in which chemotherapy was only one of many factors involved in their course. It is fair to say that pneumonia due to *B. coli* or proteus occurring in these patients is an uncommon surgical complication unless this type of organism has previously been established in the respiratory tract. Since neither patient had obvious chronic bronchitis or chronic sinusitis, the most common precursors for such gram-negative infections, it is likely that suppression of the normal gram-positive respiratory bacterial flora by penicillin was the immediate reason for the unhampered growth of coliform organisms. It is unknown whether these organisms

arrived via the blood stream, lymphatics or through regurgitation. The fact is that the patients died of overwhelming bacterial pneumonia due to these organisms.

In the last two patients, both medical problems, there was again a poor natural resistance to infection. Each had previously had many and varied acute respiratory illnesses. The justified use of penicillin for the first infection did not relieve us of the likelihood of secondary infection. In these patients accurate knowledge of the immediate status of the bacterial flora was most easily obtained by studying gram stains of sputum specimens. Prompt changing of therapy when the flora shifted was made possible by information gained in this way.

In the light of experiences herein reported it is apparent that marked adverse shifts in the bacterial flora of a viscus may be induced by powerful chemotherapeutic agents. Such adverse shifts are most likely in debilitated persons undergoing various surgical procedures or in patients with underlying poor resistance to infection as evidenced by low serum proteins, quite low white blood counts or the presence of chronic foci of infection. These untoward alterations in flora may lead to overwhelming infections within the time required for ordinary cultures to grow in the laboratory. Therefore, frequent gram-stained smears of body secretions are invaluable in following shifts from gram-positive to gram-negative organisms or in ascertaining predominating morphologic bacterial cell types.

The routine use of combined penicillin and streptomycin from the start of serious respiratory infections or the use of sulfadiazine alone because it is effective against many organisms of the gram-negative as well as the gram-positive group is not recommended. It has been pointed out that this biologic complication of penicillin therapy is unusual. It does not justify exposing the majority of persons treated with penicillin to the well known hazards of streptomycin therapy when penicillin alone is most often quite adequate. A more subtle pitfall of such

methods is not so much that specific infecting organisms are not recognized but rather that attention is directed entirely toward the bacteria-chemotherapy aspects of an illness and critical host factors are not fully evaluated. Neither is the use of sulfadiazine alone a safe refuge from accurate diagnosis. It is not as effective as penicillin against some organisms, for example staphylococcus, and it is powerless against others such as the influenza bacillus. Unfortunately it is just these organisms which are secondary invaders when host resistance is low and penicillin has altered the bacterial flora. The technical burden of frequent gram-stained smears of body secretions in such acute illnesses is no greater than taking an x-ray and it will usually yield equally valuable information when planning specific treatment.

Until the introduction of penicillin into therapy, specific chemotherapy was plagued with reasons enough for accuracy in diagnosis. A lack of clinical response could be due to an incorrect diagnosis, to inadequate dosage, to a resistant organism, to a walled-off infection, to a drug reaction. Now penicillin has added still another "drug reaction," namely, the shift in bacterial flora. This problem seems to have arisen out of the sheer effectiveness and specificity of the chemotherapeutic agent itself.

SUMMARY

1. Four recent case histories from the Peter Bent Brigham Hospital are presented in which penicillin therapy was followed by complicating pneumonia due to gram-negative organisms. Two patients, treated prophylactically during and following surgery of the gastrointestinal tract, died. Two other patients, successfully treated for pneumococcal pneumonia, developed a secondary pneumonia due to gram-negative organisms. Recovery followed prompt institution of streptomycin therapy.

2. The importance of previous chronic pulmonary disease, of general debility and of the presence of a mixed gram-positive and gram-negative flora in the cultures of

the respiratory tract before treatment is stressed in the pathogenesis of this type of infectious complication.

3. The simple gram-stained smear of the throat or sputum at the time of the sudden chill and rise in temperature during chemotherapy may permit an immediate diagnosis and prompt institution of proper drug therapy.

REFERENCES

1. ELLINGER, P. and SHATTOCK, F. M. Nicotinamide deficiency after oral administration of penicillin. *Brit. M. J.*, 2: 611-613, 1946.
2. WECKSTEIN, A. M. A bacteriologic study of the resistance of organisms isolated from cases of non-specific urethritis to three chemotherapeutic agents. *Mil. Surgeon*, 99: 312-316, 1946.
3. KLEIN, M. A mechanism for the development of resistance to streptomycin and penicillin. *J. Bact.*, 53: 463-467, 1947.
4. BECKMAN, H. and LATUM, A. L. Penicillin resistance, *Wisconsin M. J.*, 46: 621, 1947.
5. MILLER, C. P. Development of bacterial resistance to antibiotics. *J. A. M. A.*, 135: 749-751, 1947.
6. WEINSTEIN, L. The spontaneous occurrence of new bacterial infections during the course of treatment with streptomycin or penicillin. *Am. J. M. Sc.*, 214: 56-63, 1947.
7. ORY, E. M. et al. Bacteriologic studies of sputum in patients with pneumococcal pneumonia treated with penicillin. *J. Lab. & Clin. Med.*, 31: 409-422, 1946.
8. APPELBAUM, E. and LEFF, W. Occurrence of superinfections during antibiotic therapy. *J. A. M. A.*, 138: 119-121, 1948.

Aureomycin in the Treatment of Tularemia*

JOHN C. RANSMEIER, M.D., HARRY J. PRICE, M.D. and ZERNEY B. BARNES, JR., B.S.

Atlanta, Georgia

THE effectiveness of aureomycin in therapy of brucellosis and rickettsioses¹⁻⁵ suggests that it might also be useful in tularemia, since in many respects *B. tularensis* occupies a position intermediate between *Brucella* and *Rickettsia* and has properties in common with both. The low toxicity of aureomycin and its activity when administered orally would offer decided advantages should it prove efficacious in the treatment of tularemia.

Aureomycin has been shown to exert a bacteriostatic effect against *B. tularensis* *in vitro*⁶ and to possess striking suppressive power against tularemia in mice although most of the animals died after cessation of treatment.^{6,7} Complete protection was achieved against only small inocula. Experimental tularemia in the mouse is a fulminating infection with 100 per cent mortality and it is difficult to apply these results to the human disease. Woodward et al.⁷ have recently reported on three patients in whom aureomycin therapy was considered effective. Our results with aureomycin treatment of three patients with tularemia at Lawson Veterans Administration Hospital and Grady Memorial Hospital are described herein.

CASE REPORTS

CASE I. *Tularemia pneumonia:* A thirty-seven year old Negro skinned and dressed two wild rabbits on December 4, 1948. On December 9th he noted malaise followed by a shaking chill, generalized aching and headache. The following day his temperature was 102°F. Fever continued and he remained in bed. On December

13th, the fifth day of illness, he was admitted to Lawson Veterans Administration Hospital.

The patient appeared moderately ill. He was oriented but lethargic. Oral temperature was 99.6°F., pulse rate 74, respiratory rate 24 and blood pressure 100/70. There was a crusted ulceration measuring 3 mm. in diameter over the dorsal surface of the distal interphalangeal joint of the left thumb. No surrounding tenderness, erythema or edema were present. This lesion had been present since mild trauma three weeks previously. Non-tender, firm lymph nodes measuring about 1 and 1.5 cm. were palpable in the left and right axillae, respectively. Except for occasional non-productive cough, examination of the chest was negative and the rest of the physical examination was non-contributory.

Examination of the blood on the sixth day of illness revealed 7,950 leukocytes per mm.³ of which 88 per cent were neutrophils. The urine had a specific gravity of 1030; it contained no sugar and 3+ albumin. An uncentrifuged specimen showed 3 to 6 red cells, 5 to 10 white cells and a few granular casts per high power field.

On the sixth day of disease the temperature rose to 105°F. and the respiratory rate to 32. (Fig. 1.) Cough became more frequent and the patient appeared seriously ill. Although physical examination of the chest was negative, x-ray showed confluent patchy consolidation in the peripheral portion of the right upper lung field with extensive right hilar lymphadenopathy. (Fig. 2A.) The sputum smear and culture revealed only normal bacterial flora; culture for tubercle bacilli was later reported negative. Three blood cultures in tryptose phosphate broth were negative December 14th and 15th.

The presence of pneumonia associated with a history of rabbit contact suggested the diag-

* From the Department of Bacteriology and Immunology, Emory University School of Medicine, Atlanta, Ga., and the Medical Service, Lawson Veterans Administration Hospital, Chamblee, Ga. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

nosis of tularemia although the lesion on the left thumb appeared purely traumatic and there was no significant peripheral lymphadenopathy. The temperature followed a typhoidal course ranging from 103° to 105°F. without remission. On the seventh day of illness oral administration of aureomycin* was begun in doses of 1.5 Gm. every six hours for four doses, then 1 Gm. every six hours. Within twenty-four hours the temperature declined to 99.8°F. but rose again to 101°F. then dropped to 99.2°F. on the ninth day of disease. The respiratory rate fell to 20, the cough decreased and the patient was greatly improved. Although he continued to feel well except for residual weakness, the fever then began to increase daily. On the twelfth day of illness the aureomycin dosage was increased to 1.5 Gm. every six hours but the temperature continued to climb reaching 103.2°F. on the fourteenth day. The patient did not appear very ill; his cough had almost subsided. The chest remained clear to physical examination and there was little change noted in the x-ray. The leukocyte count was 4,400 per mm.³ Aureomycin was discontinued after a total dosage of 35 Gm. Within forty-eight hours the temperature dropped to normal.

The agglutination test with *B. tularensis* antigen was negative on the sixth day of illness but became positive in dilutions of 1:1280 on the fourteenth day and 1:2560 on the sixteenth day. Repeated agglutination tests with *Br. abortus* antigen were negative.

The patient continued afebrile and improved steadily. Chest x-ray on the twenty-second day (Fig. 2B) showed considerable clearing of the pulmonary consolidation and reduction in the hilar lymphadenopathy. During the fourth week convalescence was complicated by urinary obstruction resulting from an old stricture of the posterior urethra. A urine culture on the twenty-sixth day (twelve days after discontinuation of aureomycin) yielded beta hemolytic streptococci and coagulase positive staphylococci. The stricture was dilated on the twenty-eighth day, followed by a brief febrile rise to 100°F. Urinary symptoms were relieved and the patient was discharged on January 8, the thirty-first day of illness.

The possibility that the fever on the fourth to eighth days of aureomycin therapy might

have been caused by a drug reaction was considered and the patient was readmitted on January 31st. Since discharge he had felt well except for residual weakness, slight exertional dyspnea and occasional cough. Physical examination was essentially negative. The serum

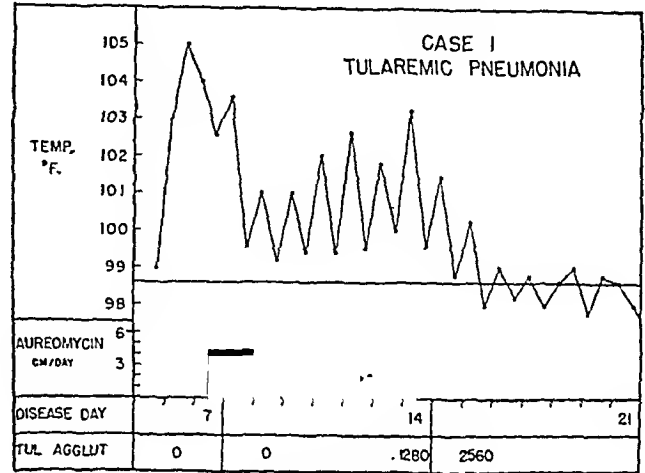


FIG. 1.

agglutinated *B. tularensis* antigen in a dilution of 1:640. The urine was negative except for 2 to 5 white blood cells per high power field in an uncentrifuged specimen. Further dilatation of the urethral stricture was not required. Chest x-ray on February 1st showed only a few delicate linear densities in the base of the right upper lobe. (Fig. 2c.) The right hilar shadow remained somewhat enlarged.

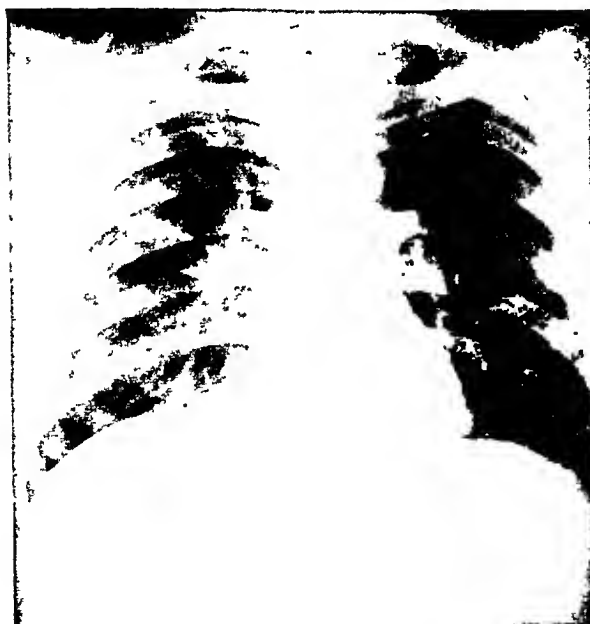
A cautious trial course of aureomycin was given beginning on January 31st with a dosage of 0.25 Gm. orally every six hours. On February 3rd the dosage was increased to 0.25 Gm. every four hours and continued until February 7th. A total of 9 Gm. was given. The patient had no symptoms and the maximum oral temperatures were 99°F. and 99.2°F. Although the dosage was smaller than that previously given for treatment, there was no evidence that the secondary rise of temperature at that time was due to sensitivity to aureomycin. The patient was well when discharged from the hospital on February 9th.

CASE II. Ulceroglandular tularemia: A thirty-three year old Negro cut his left index finger with a pocket knife about November 18, 1948. On November 20th he ate rabbit but denied handling the animal before it was cooked. His illness began abruptly on November 23rd with headache and fever, followed shortly by a shivering chill. A few hours later a second chill occurred. Next day anorexia, nausea and vomiting appeared with another chill and severe head-

* The aureomycin used in treatment of the patients reported herein was supplied by courtesy of the Lederle Laboratories Division, American Cyanamid Co.



FIG. 2A. Case I, sixth day of disease.



2B



2C

FIG. 2. B, Case I, twenty-second day of disease, C, Case I, fifty-fifth day of disease.

ache. He remained at home, and fever, weakness, aching, anorexia and occasional nausea and vomiting continued. An infected ulcer developed on the finger at the laceration site and a tender swelling appeared in the left axilla. He was admitted to Grady Memorial Hospital on December 6, the fourteenth day of illness.

The patient was acutely ill. Oral temperature was 102°F., pulse rate 112, respiratory rate 20 and blood pressure 120/80. On the left index

finger there was a crusted ulcer measuring 1 by 2 cm. without surrounding induration or tenderness. A firm tender node 2 cm. in diameter was palpable in the left axilla. Except for dental caries the remainder of the physical examination was non-contributory.

Examination of the blood revealed 19,800 leukocytes per mm.³ with 65 per cent neutrophils. The urine had a specific gravity of 1024; it contained no sugar and 2+ albumin. A centrifuged specimen showed occasional red cells and 5 to 7 white cells per high power field. Chest x-ray was negative. Two blood cultures in tryptose phosphate broth on the fourteenth day of illness and two on the fifteenth day showed no growth. Serum agglutinins for *B. tularensis* were present in a titer of 1:80 on the fifteenth day and 1:160 on the sixteenth day.

During the first forty-eight hours in the hospital the fever followed a septic course (Fig. 3), reaching a peak of 104.2°F. on the

sixteenth day of illness. Aureomycin was started orally at that time in doses of 1.5 Gm. every six hours and administered in lesser doses as shown in Figure 3 until the twenty-third day. A total of 19.5 Gm. was given.

A remarkable clinical improvement occurred after the start of aureomycin therapy. Within twelve hours the temperature dropped to normal and did not rise above 99.4°F. thereafter. Coincident with the fall in temperature

there was profuse perspiration and striking subsidence of symptoms. Malaise and aching disappeared, the appetite returned and strength was rapidly regained. Serum agglutinins for *B. tularensis* rose to 1:320 on the seventeenth day and were present in a dilution of 1:640 on the

before her husband. Streptomycin therapy was given and she recovered after a stormy course although incision and drainage of a huge fluctuant axillary abscess was necessary.

On admission the patient was only mildly ill. Oral temperature was 101.2°F., pulse rate 84,

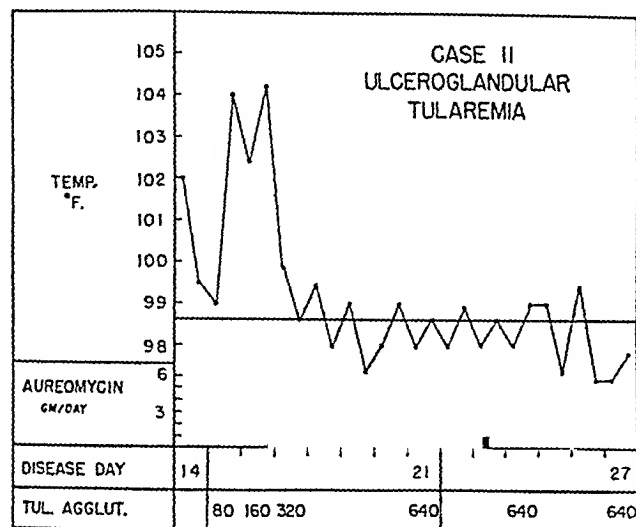


FIG. 3.

twenty-first, twenty-fourth and twenty-seventh days. On the twenty-seventh day the agglutinin titer for *Br. abortus* was 1:160. The patient was allowed out of bed on the eighteenth day and was increasingly ambulatory thereafter. The finger ulcer healed in a few days. By the twenty-fourth day the axillary node had decreased to half its original size and the patient was discharged on December 21st, the twenty-eighth day of disease. When he was seen in the outpatient clinic on January 7th, the axillary node was no longer palpable and he appeared completely recovered.

CASE III. Ulceroglandular tularemia: A forty-four year old Negro incurred an abrasion of the right index finger while hunting on November 23rd. He killed and dressed five wild rabbits. The injured finger became painful on November 26th and he developed headache, malaise and chilly sensations. Next day he was much worse and remained in bed. After three or four days the finger lesion drained a small amount of pus and a tender swelling appeared in the right axilla. Five or 6 days later there was some improvement and he was ambulatory although weakness, malaise and low-grade fever persisted until admission to Grady Memorial Hospital on December 8th, the thirteenth day of illness.

The patient's wife, who prepared and cooked the rabbits, also developed ulceroglandular tularemia on November 26th. She was extremely ill and was admitted to the hospital several days

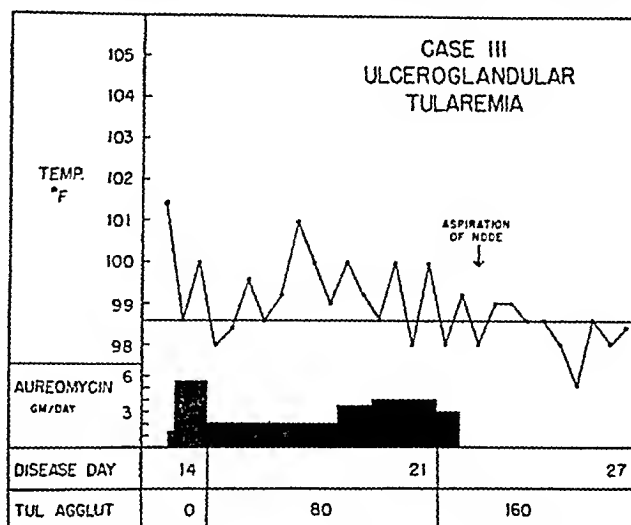


FIG. 4.

respiratory rate 22 and blood pressure 115/70. On the right index finger there was an indolent lesion measuring 1.5 by 1 cm. which was slightly elevated and indurated and covered by scaly epidermis. A tender non-fluctuant lymph node measuring 5 cm. in diameter was palpable in the right axilla. No other significant findings were noted.

The leukocyte count was 21,550 per mm.³ with 74 per cent neutrophils. Urinalysis was negative except for occasional white cells in a centrifuged specimen. Agglutination tests with *B. tularensis* antigen were negative on the thirteenth and fourteenth days of illness. Chest x-ray was negative on the thirteenth and twenty-first days.

In view of the history and clinical picture and since the patient's wife had unquestionable tularemia, a diagnosis of ulceroglandular tularemia was made. Aureomycin was started orally late on the thirteenth day of illness in dosage of 1.5 Gm. every six hours for four doses after which the dosage was reduced and continued as shown in Figure 4. Within twenty-four hours after the start of therapy the patient felt better and in forty-eight hours the temperature dropped to normal. He was asymptomatic except for tenderness in the axilla. However, on the sixteenth day of illness the temperature rose to 99.4°F. and on the seventeenth day to 101°F. Serum agglutinins for *B. tularensis* ap-

peared in a titer of 1:80 on the eighteenth day. On the nineteenth day aureomycin was increased to 1 Gm. every six hours; but since the axillary node remained tender and gradually became fluctuant, the antibiotic was discontinued on the twenty-second day. Aspiration of the node was performed on the twenty-third day and 10 ml. of pus removed. Next day the temperature dropped to normal and remained so. Agglutinins for *B. tularensis* reached a titer of 1:160 on the twenty-fourth day, with no cross agglutination of *Br. abortus* antigen. The axillary node was still palpable but the patient was otherwise asymptomatic when discharged from the hospital on December 22nd, the twenty-seventh day of illness.

The patient remained free of symptoms except for swelling and tenderness in the axilla. The node was again aspirated in the out-patient clinic on January 4th and 11th, 15 ml. of pus being removed on each occasion. On January 15th, the fifty-first day of illness, spontaneous rupture occurred after which drainage gradually subsided. By February 1st, sixty-eight days after onset, all induration in the axilla had disappeared and the patient was entirely well.

COMMENT

Streptomycin was the first chemotherapeutic agent shown to influence tularemic infection significantly in experimental animals.⁸ Aureomycin is the second substance reported to exert similar activity.^{6,7} Woodward et al.⁷ compared the action of the two antibiotics against tularemia in mice and concluded that aureomycin was more effective than streptomycin in delaying death. Three tularemia patients treated by these authors with aureomycin appeared to respond well, and evaluation in additional cases is desirable.

The course of human tularemia is notoriously variable, ranging from mild subclinical infections to overwhelming septicemia with death in a few days. Even without specific therapy the mortality in 19,208 reported cases of all types was only 7.4 per cent.⁹ The possible pitfalls in assessing therapeutic effect against this disease have been amply demonstrated over the last twenty years by passing enthusiasms for various drugs and other agents. It is there-

fore unsound to draw conclusions from the results of treatment in a few cases.

The uncomplicated ulceroglandular form of the disease is especially unsuited for therapeutic trials since the mortality is exceedingly low and the febrile course unpredictable. Suppuration and drainage of the involved nodes occur in about 50 per cent of cases.¹⁰ In the remainder there is gradual healing over a period of several weeks or months. When given to acutely ill patients with ulceroglandular tularemia, streptomycin usually produces prompt improvement in general symptoms with decrease of temperature to normal in three to six days, but its value in the treatment of glandular involvement is much less certain. Berson and Harwell¹¹ concluded that streptomycin had little effect upon such glands when given after the twelfth day of disease.

As pointed out by Francis,⁹ the more severe pulmonary form of tularemia provides a better test of a chemotherapeutic agent; it was in treatment of such patients that the value of streptomycin was firmly established. Streptomycin has reduced the mortality of tularemic pneumonia from about 40 per cent¹² to a very low figure.^{9,11,13} It produces striking relief of symptoms in twenty-four to forty-eight hours and in most cases the temperature falls to normal within three to seven days. Several weeks may be required for complete clearing of pulmonary lesions as seen on x-ray.

Aureomycin treatment was followed in all three patients presented herein by definite subjective improvement and a drop in temperature within twenty-four hours after starting therapy. At the end of forty-eight hours in all three cases the temperature approached normal levels. In Case 1, however, the temperature gradually rose during the next five days to 103.2°F. and fell to normal only forty-eight hours after discontinuation of therapy. Nevertheless the patient showed striking subjective and objective improvement, and the pneumonic process resolved much more quickly than would have been expected without specific therapy. There was no pleural effusion.

This patient's condition was complicated by a urethral stricture and low-grade urinary tract infection.

Case II was an uncomplicated case of ulceroglandular tularemia in which the patient was acutely ill on the sixteenth day when aureomycin treatment was started. Striking improvement occurred within twelve hours. Although the probable course of such a case could not be predicted, it would be most unusual to see such rapid subsidence of fever and symptoms without specific therapy.

Case III was a mildly ill patient with ulceroglandular tularemia in whom aureomycin therapy was started on the thirteenth day of illness. Subjective improvement and an initial fall in temperature occurred but later he ran a low-grade fever despite continued therapy. Aureomycin obviously had no effect upon the axillary node which became fluctuant during therapy and required aspiration on three occasions. Healing finally occurred after spontaneous rupture and drainage of the gland on the fifty-first day of disease.

No significant toxic reaction occurred in these patients during or after aureomycin treatment. Although drug fever was suspected in Case I, readministration of the antibiotic failed to produce a febrile reaction. In Case III there was slight stimulation of bowel action resulting in two to three soft stools daily during aureomycin therapy. This patient also showed 1 to 2+ albuminuria on the fifth to seventh days of therapy. Centrifuged urine specimens contained 1 to 5 red cells and 1 to 5 white cells per high power field, with an occasional white cell cast. Urinalyses at two-day intervals revealed no further albuminuria and the cellular elements rapidly disappeared. There were no significant blood changes and none of the patients complained of anorexia, nausea or vomiting.

Although it is difficult to predict the course of tularemia without specific therapy in individual cases, we believe that two of our patients (Cases I and II) were impressively benefited by aureomycin. Certainly

aureomycin exerted no action on glandular suppuration in Case III but streptomycin has also failed in similar cases. Our results and those of Woodward et al.⁷ encourage further trial of aureomycin in human tularemia. At present the optimal dosage and duration of treatment are unknown, and available data are insufficient to permit a sound clinical comparison with streptomycin in the treatment of this disease. Proper evaluation of aureomycin will not be possible until more patients have been treated, including a number of cases with pulmonary involvement.

SUMMARY

1. A patient with tularemic pneumonia and one with ulceroglandular tularemia improved strikingly after oral aureomycin therapy and recovered rapidly.
2. Another patient with ulceroglandular tularemia treated on the twelfth day of illness improved subjectively but aureomycin did not prevent glandular suppuration.
3. Further evaluation of aureomycin in human tularemia is indicated.

REFERENCES

1. SCHOENBACH, E. B., BRYER, M. S. and LONG, P. H. The pharmacology and clinical trial of aureomycin: a preliminary report. *Ann. New York Acad. Sc.*, 51: 267-279, 1948.
2. SPINK, W. W., BRAUDE, A. I., CASTANEDA, M. R. and GOYTIA, R. S. Aureomycin therapy in human brucellosis due to *Brucella melitensis*. *J. A. M. A.*, 138: 1145-1148, 1948.
3. KNIGHT, V., RUIZ-SANCHEZ, F., RUIZ-SANCHEZ, A. and McDERMOTT, W. Aureomycin in typhus and brucellosis. *Am. J. Med.*, 6: 407-416, 1949.
4. ROSS, S., SCHOENBACH, E. B., BURKE, F. G., BRYER, M. S., RICE, E. C. and WASHINGTON, J. A. Aureomycin therapy of Rocky Mountain spotted fever. *J. A. M. A.*, 138: 1213-1216, 1948.
5. SCHOENBACH, E. B. Aureomycin therapy of recrudescence epidemic typhus (Brill's disease). *J. A. M. A.*, 139: 450-452, 1949.
6. RANSMEIER, J. C. The effect of aureomycin against *Bacterium tularensis*. (In press.)
7. WOODWARD, T. E., RABY, W. T., EPPES, W., HOLBROOK, W. A. and HIGHTOWER, J. A. Aureomycin in treatment of experimental and human tularemia. *J. A. M. A.*, 139: 830-832, 1949.
8. HEILMAN, F. R. Streptomycin in the treatment of experimental tularemia. *Proc. Staff Meet., Mayo Clin.*, 19: 553-559, 1944.

9. FRANCIS, E. Streptomycin in treatment of tularemia. *Tr. A. Am. Physicians*, 60: 181-186, 1947.
10. FRANCIS, E. Tularemia. In Tice's Practice of Medicine. Vol. 3, pp. 663-678. 1944.
11. BERSON, R. C. and HARWELL, A. B. Streptomycin in the treatment of tularemia. *Am. J. M. Sc.*, 215: 243-249, 1948.
12. STUART, B. M. and PULLEN, R. L. Tularemic pneumonia. Review of American literature and report of 15 additional cases. *Am. J. M. Sc.*, 210: 223-236, 1945.
13. HUNT, J. S. Pleuropulmonary tularemia: observations on 12 cases treated with streptomycin. *Ann. Int. Med.*, 26: 263-276, 1947.
14. HOWE, C., CORIELL, L. L., BOOKWALTER, H. L. and ELLINGER, H. V. Streptomycin treatment in tularemia. *J. A. M. A.*, 132: 195-200 1946.

Newer Concepts of the Role of Potassium in Disease*

T. S. DANOWSKI, M.D.

Pittsburgh, Pennsylvania

WITHIN the last few years a considerable amount of new data has been accumulated on potassium, one of the chief cations in the body. Much of this has been based on balance studies and as such represents a fundamental contribution to our knowledge of this electrolyte in various physiologic and clinical situations. Nonetheless, there is still no adequate explanation of how or why tissue cells acquire and maintain concentrations of potassium in excess of those in interstitial fluid and serum. Even though the mechanism of this unequal distribution remains a challenge, the newer findings identify factors which influence concentrations and total amounts of body potassium. Their importance can perhaps be best emphasized by presentation against the background of previous knowledge and beliefs.

EXTRACELLULAR POTASSIUM

Hyperkalemia, Its Origin and Significance.

It has been known that under ordinary conditions the potassium levels in extracellular fluid vary to only a limited extent. In a healthy fasting individual the upper limit of this range is about 5.5 mEq./L. In certain instances this may be exceeded and not necessarily indicate any abnormality. Thus ingestion of potassium salts can increase, temporarily at least, serum concentrations of this ion above 5.5 mEq./L.¹ High serum levels have also been observed in the course of potassium balance studies conducted in diabetic and non-diabetic

subjects.^{2,3} Such increments of potassium in the extracellular fluid are soon eliminated by the kidneys in those subjects whose body stores of this cation are intact. The extra potassium may be excreted immediately or it may enter certain cells, such as those of the liver or muscle, for a temporary sojourn. In a matter of hours this portion of the administered potassium re-enters the interstitial fluid and is in turn excreted by the nephrons.⁴ Recent work has shown that two mechanisms exist whereby this may be accomplished. Not only, as previously recognized, is potassium removed by glomerular filtration but under certain circumstances excretion through the renal tubules can be unequivocally demonstrated.^{5,6}

The processes whereby undue and dangerous rises in extracellular potassium can be mitigated or prevented may prove inadequate under some conditions. It is possible, for example, to inject potassium rapidly enough by vein to produce toxic concentrations in serum, overtaking the physiologic adjustments which have been described to these extra supplies of the cation.⁷ On the other hand, similar degrees of hyperkalemia may be observed in disease states with usual or even limited intakes of potassium. These rises may result from the following, alone or in combination: (1) contraction of the volume of extracellular fluid, (2) inability of the cells to take up potassium, (3) transfers of cell potassium to the extracellular compartment and (4) inadequate renal excretion. All these factors,

* From the Department of Research Medicine, the Renziehausen Foundation, and the Children's and Presbyterian Hospitals of the University of Pittsburgh School of Medicine, Pittsburgh, Pa.

with the possible exception of (3), may be operative for example in producing the hyperkalemia of untreated adrenal cortical insufficiency.⁸ The role of these various processes in renal insufficiency remains unsettled. As a matter of fact, until recently it has appeared as if potassium intoxication in renal failure occurred only in subjects with complete suppression of urine formation. This belief has been based on the readiness with which experimental animals with anuria following bilateral nephrectomy or ureteral ligation died of potassium poisoning.⁹ Similar occurrences were thought to be rare in patients with terminal chronic nephritis, presumably either because failing kidneys still excreted potassium or because cells of the body failed to release, or even took up potassium.¹⁰ Recent studies have indicated, however, that potassium poisoning can be demonstrated in a minority of such patients if they are kept under constant surveillance up to the moment of death.¹¹ These findings did not appear to be agonal since serial observations revealed the gradual evolution of the changes known to occur with potassium intoxication. These were succinctly described in 1938 by Winkler, Hoff and Smith in experimental studies on dogs.¹² In the most characteristic form the electrocardiogram changed progressively as the serum potassium level rose. In the initial phases the T wave increased in height. This was followed by broadening of the QRS complex with loss of the ordinary contours, changes in the S-T and T segments and disappearance of the P wave. Ultimately the heart stopped in diastole. In observations on humans an increase in the height and a sharpening of the contour of the T waves were also the earliest changes detectable as the potassium concentration in serum rose; subsequent heart block has been observed as well.¹¹

To date, therefore, poisoning due to increased levels of extracellular potassium appears to be a problem only in patients who are receiving this cation in undue amounts or in a minority of those with renal failure. The potassium levels in untreated

Addison's disease usually do not attain the lethal range. It is possible, however, that in agonal states in these subjects and in others potassium in extracellular fluid rises to toxic concentrations. This is logical in view of the marked increase found at postmortem. This would suggest that with impending death and disruption of the ordinary physiologic barriers which restrain cell potassium from pouring out into extracellular fluid this change may appear premortem.

Occurrence and Effects of Hypopotassemia. In contrast to hyperkalemia decreased levels of serum potassium have been recorded under a great variety of clinical conditions. The lower limit of normal in adults appears to be about 3.5 mEq./L. Abnormally low levels of extracellular potassium can, on theoretical grounds, result from: (1) dilution by low potassium fluids, (2) losses of the cation in urine or other body fluids or (3) transfers of potassium into cells. Obviously an inadequate intake of potassium will maintain the low concentrations produced by these aforementioned processes.

All of these factors may be operative in the development of low serum potassium levels during recovery from diabetic acidosis and coma.^{2,13} Such patients usually develop anorexia and vomiting during the early phases of their illness.¹⁴ As a consequence the intake of potassium is reduced essentially to zero. At the same time considerable amounts of potassium are lost in the gastric secretions and in the urine.¹⁵⁻¹⁷ Even though the body stores of this electrolyte are considerably depleted in these various ways, the patients are frequently admitted with elevated or normal concentrations of potassium in serum.^{2,13,18} This is explicable, in part at least, by the attendant contraction of the plasma and extracellular volumes as a result of dehydration. With administration of large amounts of potassium-free fluids, such as saline and subsequently glucose solutions, the volume of body water is re-expanded. At the same time potassium moves into cells under the impetus of insulin, restoration of carbohydrate catabo-

lism, glycogen deposition and protein formation. While these processes are going on, further amounts of potassium are lost in the urine. The magnitude of these losses tends to diminish, however, during convalescence until in some instances urine:plasma potassium ratios lower than 1.0 are encountered.¹⁹ As a consequence of these various factors hypopotassemia develops in almost all patients during the early phases of the hitherto standard treatment of diabetic acidosis with parenteral fluids.

Balance studies similar to those conducted in diabetic acidosis and coma have served to define, in part, the chain of events which results in low serum potassium values in infants with pyloric obstruction and prolonged vomiting.^{3,20} Although actual measurements during the prehospitalization phase of such subjects are not available, it seems highly probable that the loss of potassium in vomitus is of considerable magnitude. This is, of course, accompanied by a greatly reduced intake of potassium in food. On admission these patients are frequently found to have hypopotassemia in addition to hypochloremia, high serum bicarbonate levels and deficits of body water. It is true that at the time of admission, or shortly thereafter, losses of potassium in the urine are quite low.^{3,19} This does not exclude the possibility that earlier losses via this route were of greater magnitude. The usual therapy with low potassium fluids, while oral feedings are withheld, either produces or further aggravates hypopotassemia.

Some of these same mechanisms account for the low serum potassium values found in many adult subjects with gastrointestinal disorders.^{21,22} Again the combination of starvation and electrolyte losses in gastric or intestinal secretions is present. Such individuals, in contrast to the infants just described, continue to lose considerable amounts of potassium in the urine. Frequently the losses via this route exceeds those in vomitus. Replacement therapy has heretofore not included the use of fluids which contain adequate amounts of potassium.

When abnormally low levels of serum potassium develop in such subjects, they are usually referable to a combination of these factors. Renal losses, however, appear to play a predominant role.

Similarly, although confirmatory studies are lacking, it is by inference continued and perhaps excessive renal loss that is responsible for the low serum potassium values seen, surprisingly enough in view of the earlier discussion, in certain patients with renal disorders.²²⁻²⁵ These may represent instances in which the glomerular filtration of potassium is well maintained while tubular reabsorption is considerably impaired. Unfortunately complete and prolonged balance studies are not available in the cases cited and hence no statement is possible as to the role of inanition, vomiting and fluid administration which frequently accompany renal failure. Similar decreases in the potassium level can be produced, of course, by peritoneal lavage, intestinal perfusion or by means of the artificial kidney using fluid low in potassium.

Up to this time only one category of potassium disorders has been identified in which the decline in extracellular concentration is entirely or almost entirely explicable by a transfer into cells. This is true of periodic paralysis in which serum potassium falls abruptly, concomitant with a *decreased* urinary loss at a time when there is no evidence that extracellular volume has expanded.^{26,27} It must result, therefore, from a migration of potassium into cells.

Finally, certain associations must be mentioned since they may represent cause and effect. Thus clinical or experimental alkalosis and hypokalemia are concomitantly observed. This has been described in the alkalosis of Cushing's disease, during DOCA intoxication, in anorexia nervosa and in subjects with chronic losses of gastric secretions. The simultaneous occurrence of these two changes is much too frequent to represent chance and suggests, particularly in view of Darrow's experiments,³² a more fundamental relationship. However, since in all of these disorders the extracellular

and cell potassium values are apt to be low rather than normal or high, it is obvious that at least the initial decrease occurred through losses in urine or other body fluids. Their continuance can be assigned either to some type of depressant effect of alkalosis on potassium levels or possibly to an inability to replace deficits because of the continued urinary loss of the ion.

The physiologic effects of the low serum and extracellular fluid potassium values appears, insofar as is now known, to be limited to electrocardiographic changes in S-T and T waves and to the occasional production of a reversible and usually non-fatal muscular paralysis. The latter characteristically occurs, by definition, in idiopathic periodic paralysis and is often seen in the other disorders which have been mentioned. The fact that it is not an invariable occurrence emphasizes the need for a flexible concept in predicting the effects of hypopotassemia. This is in accord with what is known of the physiology of this ion. Thus the deposition of protein, of glycogen or continued carbohydrate metabolism will remove potassium from serum and may lower its concentration in the extracellular fluid.³³⁻³⁵ Since this is not productive of paralysis, it is obvious that a certain range of physiologic variation is present. The degree to which this must be exceeded to produce paralysis apparently differs not only from disease to disease but also from subject to subject.

It is more than probable, therefore, that the chief importance of hypopotassemia lies in the fact that it is frequently associated with deficits of cell potassium rather than that it may produce muscular paralyzes or electrocardiographic alterations. It should be emphasized, however, that cell potassium deficits need not be accompanied by hypopotassemia.

CELLULAR POTASSIUM

General Considerations. Thus far the discussion has centered about the potassium present in interstitial fluid and serum. The inaccessibility of the cellular phase of body

water for analyses and the difficulties inherent in measuring changes in the composition of cells account for the relative paucity of data concerning intracellular potassium. This is unfortunate because the great bulk of the body stores of this cation is, of course, in cells. The concentrations there are about twenty-fold greater than those in serum. Cell potassium, furthermore, is only partially ionized and hence not all of it is osmotically active. Some is bound to protein in a characteristic ratio to cell nitrogen³³ and some is in all probability combined with phosphate or other complexes. The separate fractions of cell potassium may vary in amount. As cell protein is broken down, for example, potassium bound to this constituent is released to the extracellular fluid.³⁶ The process is reversed during a period of positive nitrogen balance. In an analogous manner, with water deprivation some of the potassium of cells not associated with protein moves to the interstitial fluid. This, of course, alters the respective osmotic forces and water enters the extracellular phase and mitigates the dehydration there.³⁷ With rehydration this portion of potassium is reconstituted. Movements of potassium into interstitial fluid, on the other hand, must accompany liver deglycogenation since it is known that during the formation of glycogen, potassium is deposited in a predictable ratio with the polymerized glucose.³⁴ Potassium also leaves muscle cells during exercise and enters the extracellular pool.³⁸ This fraction, losing its identity among the general body stores, may then enter the liver and other tissue cells, or it may be excreted in the urine. An obvious corollary to this process must be the re-entry of an equal amount of the cation into the muscle to replenish the original supplies present there. It is also known that the potassium stores in cells can be altered experimentally and clinically under a variety of conditions including dehydration, hypertonicity, oliguria and electrolyte administration.³⁹ In some but not all of these balance studies evidence was present of a reciprocal exchange of cell

potassium for sodium. Undoubtedly there still are other factors operative which have not as yet been identified or defined.

Increases in Cell Potassium and Their Apparent Benignity. Temporary increases in cell potassium following ingestion or injection of potassium salts may be looked upon as a physiologic adjustment. This can be demonstrated readily by following the distribution of administered potassium chloride. The apparent volume of body water through which the ion is dispersed continues to rise until it exceeds the value ordinarily assigned to extracellular fluid and approaches that of total body water. Subsequently potassium leaves the cells and re-enters the interstitial compartment.⁴ It is also known, for example, that adrenal cortical insufficiency is associated with increases in the amounts of cell potassium in addition to hyperpotassemia.⁴⁰ Experimentally it has been shown that chronic acidosis in non-diabetic animals is accompanied by a slight rise in the content of cell potassium.³² In periodic paralysis, too, potassium leaves serum and enters cells. Quantitatively these transfers are not necessarily large.²⁷ For practical purposes these conditions exhaust the known examples of temporary or persistent rises in cell potassium.

It is not possible to state whether or not these increases in cell potassium are in any way harmful. There is no evidence that the temporary penetration of administered potassium ions into cells produces any symptoms. Moreover, as far as is known, none of the clinical manifestations of Addison's disease are explicable on this basis. Such a possibility has not, however, been excluded. The paralytic phase of periodic paralysis appears to be related, as has already been mentioned, to the decrease in extracellular potassium and not to the rise in the intracellular fraction. It may well be that the absence of definite symptoms or manifestations with increases in the total amount of cellular potassium is related to the fact that the concentrations of osmotically active potassium are maintained at a constant. At least two mechanisms exist whereby this

adjustment can be made: (1) water can move into the cells in response to osmotic forces whenever the osmotically active portion of this cation increases and (2) potassium which enters the cells may be rendered osmotically and perhaps physiologically inert by becoming bound to anion constituents.^{34,41}

To date, depletion of intracellular potassium has been demonstrated by balance studies in a variety of conditions. It has been shown, for example, that during the early phases of the treatment of diabetic acidosis or coma the patients continue to lose potassium from cells.^{2,13} To avoid confusion it must be emphasized that this statement refers to the net balance of cell potassium because it is known that with administration of insulin and the resumption of carbohydrate metabolism potassium re-enters cells. These findings must indicate that at that time certain cells are regaining potassium while others are still losing this electrolyte. Losses of cell potassium have also been recorded by Elkinton and his co-workers during the balance studies cited earlier in subjects with gastrointestinal disorders²² and by Darrow in infants with diarrhea.^{42,43} These negative balances of cell potassium were in excess of any losses of this cation which could be attributed to breakdown of cell protein. In all of these conditions any loss of cell potassium to the extracellular compartment must have been accompanied by comparable or greater losses of potassium from the body in urine, vomitus, drainage fluids or excreta. Otherwise the concentration of potassium would have risen to dangerous levels in extracellular fluid. Retention of administered potassium by cells has been observed in these various clinical states as well as in infants convalescent from prolonged vomiting.³ These findings have been interpreted as indicative of deficits of cell potassium; as already mentioned, injected or ingested potassium salts are not retained to the same degree, if at all, by non-depleted subjects.

It may well be that such extensive losses of cell potassium jeopardize survival. In

experimental studies degenerative changes have been observed in the myocardium following production of deficits of cell potassium by means of a low potassium diet or DCA administration.⁴⁴ Moreover, it has been possible to demonstrate by potassium therapy a definitely lowered mortality rate in infant diarrhea. In view of these findings it is not unreasonable to suggest that cellular deficits of potassium may also contribute to the mortality in various other clinical disorders. The actual mechanisms through which these harmful effects are mediated have not been identified. Presumably they are manifestations of interferences with cellular processes as a result of losses of essential constituents. This lack of knowledge by no means minimizes our responsibility in seeking, recognizing, studying and treating potassium deficiency states.

SUMMARY

An attempt has been made to integrate new findings relevant to potassium metabolism in health and disease with previously known facts. Particular emphasis has been placed on the clinical significance of increments and decrements in the extracellular and cellular fractions of this electrolyte.

REFERENCES

1. KEITH, N. M. and OSTERBERG, A. E. The human tolerance for potassium. *Proc. Staff. Meet., Mayo Clin.*, 21: 385, 1946.
2. DANOWSKI, T. S., PETERS, J. H., RATHBUN, J. C., QUASHNOCK, J. M. and GREENMAN, L. Studies in diabetic acidosis and coma with particular emphasis on the retention of administered potassium. *J. Clin. Investigation*, 28: 1, 1949.
3. DANOWSKI, T. S., AUSTIN, A. C., GOW, R. C., MATEER, F. M., WEIGAND, F. A., PETERS, J. H. and GREENMAN, L. Biochemical studies in infants following vomiting. Unpublished data.
4. WINKLER, A. W. and SMITH, P. K. The apparent volume of distribution of potassium injected intravenously. *J. Biol. Chem.*, 124: 589, 1938.
5. MUDGE, G. H., FOULKS, J. and GILMAN, A. The renal excretion of potassium. *Proc. Soc. Exper. Biol. & Med.*, 67: 545, 1948.
6. BERLINER, R. W. and KENNEDY, T. J., JR. Renal tubular secretion of potassium in normal dogs. *Proc. Soc. Exper. Biol. & Med.*, 67: 542, 1948.
7. GOVAN, C. D., JR. and WEISETH, W. M. Potassium intoxication. Report of an infant surviving a serum potassium level of 12.27 millimoles per liter. *J. Pediat.*, 28: 550, 1946.
8. WINKLER, A. W., HOFF, H. E. and SMITH, P. K. Toxicity of potassium in adrenalectomized dogs. *Am. J. Physiol.*, 133: 494, 1941.
9. HOFF, H. E., SMITH, P. K. and WINKLER, A. W. The cause of death in experimental anuria. *J. Clin. Investigation*, 20: 607, 1941.
10. DANOWSKI, T. S. and ELKINTON, J. R. Sodium and Potassium Metabolism in Disease. In press. Philadelphia. F. A. Davis Co.
11. ELKINTON, J. R., TARAIL, R. and PETERS, J. P. Transfers of potassium in renal insufficiency. *J. Clin. Investigation*, 28: 378, 1949.
12. WINKLER, A. W., HOFF, H. E. and SMITH, P. K. Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride. *Am. J. Physiol.*, 124: 478, 1938.
13. GREENMAN, L., MATEER, F. M., GOW, R. C., PETERS, J. H. and DANOWSKI, T. S. The origin of hypokalemia during diabetic acidosis or coma. *J. Clin. Investigation*, in press.
14. DANOWSKI, T. S., WINKLER, A. W. and PETERS, J. P. Salt depletion, peripheral vascular collapse, and the treatment of diabetic acidosis. *Yale J. Biol. & Med.*, 18: 405, 1946.
15. AUSTIN, J. H. and GAMMON, G. D. Gastric secretion after histamine: sodium and potassium content and pepsin estimation. *J. Clin. Investigation*, 10: 287, 1931.
16. INGRAHAM, R. C. and VISSCHER, M. B. Inverse concentration ratios for sodium and potassium in gastric juice and blood plasma. *Proc. Soc. Exper. Biol. & Med.*, 30: 464, 1932.
17. ATCHLEY, D. W., LOEB, R. F., RICHARDS, D. W., JR., BENEDICT, E. M. and DRISCOLL, M. E. On diabetic acidosis. A detailed study of electrolyte balances following the withdrawal and reestablishment of insulin therapy. *J. Clin. Investigation*, 12: 297, 1933.
18. NADLER, C. S., BELLET, S. and LANNING, M. Influence of the serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. *Am. J. Med.*, 5: 838, 1948.
19. MATEER, F., GREENMAN, L., PETERS, J. H., GOW, R. C. and DANOWSKI, T. S. Occurrence of potassium U/P ratios lower than 1.0. *Federation Proc.*, 8: 107, 1949.
20. DANOWSKI, T. S., GREENMAN, L., PETERS, J. H., GOW, R. and MATEER, F. Metabolic studies in infants during recovery from vomiting. *J. Clin. Investigation*, in press.
21. TARAIL, R. and ELKINTON, J. R. Potassium deficiency and the role of the kidney in its production. *J. Clin. Investigation*, 27: 557, 1948.
22. TARAIL, R. and ELKINTON, J. R. Potassium deficiency and the role of the kidney in its production. *J. Clin. Investigation*, 28: 99, 1949.
23. BROWN, M. R., CURRENS, J. H. and MARCHAND, J. F. Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis. *J. A. M. A.*, 124: 545, 1944.
24. MUDGE, G. H. Muscle electrolytes in patients with potassium depletion. *J. Clin. Investigation*, 27: 550, 1948.

25. SHERRY, S., EICHNA, L. W. and EARLE, D. P., JR. The low potassium syndrome in chronic nephritis. *J. Clin. Investigation*, 27: 556, 1948.
26. TALBOTT, J. H. Periodic paralysis; a clinical syndrome. *Medicine*, 20: 85, 1941.
27. DANOWSKI, T. S., ELKINTON, J. R., BURROWS, B. A. and WINKLER, A. W. Exchanges of sodium and potassium in familial periodic paralysis. *J. Clin. Investigation*, 27: 65, 1948.
28. WILLSON, D. M., POWER, M. H. and KEPLER, E. J. Alkalosis and low plasma potassium in a case of Cushing's syndrome; a metabolic study. *J. Clin. Investigation*, 19: 701, 1940.
29. KEPLER, E. J., SPRAGUE, R. G., CLAGETT, O. T., POWER, M. H., MASON, H. L. and ROGERS, H. M. Adrenal cortical tumor associated with Cushing's syndrome. Report of a case with metabolic studies and remarks on the pathogenesis of Cushing's syndrome. *J. Clin. Endocrinol.*, 8: 499, 1948.
30. FERREBEE, J. W., PARKER, D., CARNES, W. H., GERITY, M. K., ATCHLEY, D. W. and LOEB, R. F. Certain effects of desoxycorticosterone; the development of "diabetes insipidus" and the replacement of muscle potassium by sodium in normal dogs. *Am. J. Physiol.*, 135: 230, 1941.
31. SUNDERMAN, F. W. and ROSE, E. Studies in serum electrolytes. xvi. Changes in the serum and body fluids in anorexia nervosa. *J. Clin. Endocrinol.*, 8: 209, 1948.
32. DARROW, D. C., SCHWARTZ, R., IANNUCCI, J. F. and COVILLE, F. The relation of serum bicarbonate concentration to muscle composition. *J. Clin. Investigation*, 27: 198, 1948.
33. HASTINGS, A. B. and EICHELBERGER, L. The exchange of salt and water between muscle and blood. i. The effect of an increase in total body water produced by the intravenous injection of isotonic salt solutions. *J. Biol. Chem.*, 117: 73, 1937.
34. FENN, W. O. The deposition of potassium and phosphate with glycogen in rat livers. *J. Biol. Chem.*, 128: 297, 1939.
35. DANOWSKI, T. S. The transfer of potassium across the human blood cell membrane. *J. Biol. Chem.*, 139: 693, 1941.
36. ELKINTON, J. R. and WINKLER, A. W. Transfers of intracellular potassium in experimental dehydration. *J. Clin. Investigation*, 23: 93, 1944.
37. WINKLER, A. W., DANOWSKI, T. S., ELKINTON, J. R. and PETERS, J. P. Electrolyte and fluid studies during water deprivation and starvation in human subjects, and the effect of ingestion of fish, of carbohydrate, and of salt solutions. *J. Clin. Investigation*, 23: 807, 1944.
38. FENN, W. O. The fate of potassium liberated from muscles during activity. *Am. J. Physiol.*, 127: 356, 1939.
39. ELKINTON, J. R., WINKLER, A. W., and DANOWSKI, T. S. Transfers of cell sodium and potassium in experimental and clinical conditions. *J. Clin. Investigation*, 27: 74, 1948.
40. HARRISON, H. E. and DARROW, D. C. The distribution of body water and electrolytes in adrenal insufficiency. *J. Clin. Investigation*, 17: 77, 1938.
41. ELKINTON, J. R., WINKLER, A. W. and DANOWSKI, T. S. Inactive cell base and the measurement of changes in cell water. *Yale J. Biol. & Med.*, 17: 383, 1944.
42. DARROW, D. C. The retention of electrolyte during recovery from severe dehydration due to diarrhea. *J. Pediat.*, 28: 515, 1946.
43. DARROW, D. C., PRATT, E. L., FLETT, J., JR., GAMBLE, A. H. and WIESE, H. F. Disturbances of water and electrolytes in infantile diarrhea. *J. Pediat.*, 3: 129, 1949.
44. DARROW, D. C. and MILLER, H. C. The production of cardiac lesions by repeated injections of desoxycorticosterone acetate. *J. Clin. Investigation*, 21: 601, 1942.

Aureomycin in the Treatment of Infectious Diseases*

HARRY M. ROSE, M.D. and YALE KNEELAND, JR., M.D.
New York, New York

IN the year which has elapsed since the first published report of aureomycin this new antibiotic has been the subject of widespread interest to the profession and an astonishingly large volume of literature about it, both experimental and clinical, has already appeared in print. Indeed the published data are now so voluminous and the antibiotic so widely used that a general review article seems fully warranted.

Credit for the discovery of this new therapeutic agent goes to Duggar¹ who isolated and described a new species of the Actinomycetes, named by him *Streptomyces aureofaciens*, which possessed the antibiotic properties to be described hereafter. At a certain stage in its growth this micro-organism produces the antibiotic substance which is of a faintly golden-yellow color. Preliminary tests demonstrated its activity against a wide bacterial spectrum and warranted the intense efforts of Duggar and his colleagues further to explore its possibilities. Some of its chemical properties have now been described.² It is a weakly basic compound containing both nitrogen and non-ionic chlorine. The hydrochloride has an approximate solubility in water of 14 mg./ml. at 25°C., and the pH of the aqueous solution is 2.8–2.9.

Pharmacology. Studies of the pharmacologic effect of the drug have been reported by Harned et al.³ With oral administration mice tolerated 1,500 mg. per kg. and rats 3,000 mg. per kg. The LD₅₀ intravenously

for mice was 134 mg. per kg., and dogs, cats, rabbits, guinea pigs and mice tolerated intravenous doses of 50 mg. per kg. without symptoms. Chronic toxicity experiments indicated that mice, rats and dogs tolerated oral doses of 100–200 mg. per kg. daily for twelve weeks without ill effects. Generally speaking, no pathologic changes could be determined in any of the viscera studied. No evident effects on cardiac activity, liver function or kidney function (apart from a mild diuretic action) were demonstrable. The drug did not appear to influence vasomotor responses or blood sugar levels and it had no antipyretic effect in rabbits. All in all, these animal experiments indicated the likelihood of a wide margin of safety for human administration; indeed early experiences proved this to be the case.

Side Effects in Man. Oral administration of aureomycin is frequently accompanied by nausea and occasionally by vomiting and a metallic taste in the mouth. Females appear more susceptible than males; more than half of the women patients may be quite distressed by these manifestations although their intensity usually diminishes if treatment is continued. The drug also has a slightly laxative action and the passage of an increased number of soft, bulky stools is frequently observed. True diarrhea is extremely rare. It was reported by Lennette et al.⁴ that pruritus and soreness of the scrotum occurred in two patients. We have observed three instances of transitory vagi-

* From the Departments of Medicine and Bacteriology, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y.

nititis and a small number of cases of glossitis. One questionable instance of drug fever was reported by Collins.⁵

Wright et al.⁶ in an early communication described hypochromic anemia accompanying parenteral administration of the drug in a "special diluent." When this diluent was replaced by normal salt the anemia was no longer encountered. It has not been described since nor have there been any published reports of neutropenia. In this clinic, however, one case of complete neutropenia occurred in a dermatologic patient after prolonged administration of aureomycin. Return of the polymorphonuclear leukocytes took place promptly after the drug was stopped, and when it was readministered several weeks later it had no effect on the white blood cells although daily treatment was again given for a long period of time. Toxic effects on the liver, kidney and other organs have not been described.

Experimental Studies in Vitro. Aureomycin has a wider range of activity than any other antibiotic thus far discovered, with the possible exception of chloromycetin. It is effective against numerous gram-positive and gram-negative bacteria, all species of pathogenic rickettsiae, several viral agents and possibly certain protozoa.

Crystalline aureomycin hydrochloride is stable in the dry state and will maintain its potency for many months at 20–25°C. In solution, however, it deteriorates more or less rapidly depending upon the pH, the temperature and the composition of the solvent. Unbuffered solutions of the drug in distilled water at pH 2.9 have been maintained at $\pm 4^\circ\text{C}$. for twenty-three days with no measurable loss of activity, according to Dornbush and Pelcak.⁷ However, studies by Chandler and Bliss⁸ and by Paine et al.⁹ have shown that the drug becomes quite unstable at a neutral or alkaline pH, even at 4°C ., and that this instability is increased progressively as the temperature is raised to 37°C . and above. In fact, Bliss and Chandler¹⁰ found that at pH approximately 7.0 about 60 per cent of the activity was lost

in eighteen hours at 37°C . while 75 per cent was lost after four hours at 56°C . In addition to progressive loss of activity, Paine et al.⁹ demonstrated that the drug is initially less bacteriostatic at an alkaline reaction than it is at an acid reaction—the reverse of what is true for streptomycin. Price et al.¹¹ and others have found that the bacteriostatic properties of the drug are also adversely affected by many ingredients of culture media such as meat infusion, various peptones, yeast extract, whole blood, fresh or heat-inactivated serum, phosphate buffer and even sodium chloride. These facts must be borne in mind when one attempts to appraise the results of laboratory tests for the *in vitro* sensitivity of bacteria or to evaluate drug levels in blood or other body fluids as determined by different methods.

Generally speaking, *in vitro* tests have shown that aureomycin is somewhat less effective than penicillin against gram-positive bacteria and that its action is approximately the same or somewhat inferior to streptomycin against most gram-negative bacteria. Bliss and Chandler¹⁰ found that strains of *Str. hemolyticus*, *Str. faecalis*, *D. pneumoniae* and *Staph. aureus* were inhibited by 1.25 μg . or less per ml while *E. coli*, *A. aerogenes* and *K. pneumoniae* required from 1.25 to 5.0 μg . per ml. Similarly, Paine et al.¹² reported that the bacteriostatic concentrations for hemolytic streptococci, pneumococci, gonococci and meningococci did not exceed 1.0 μg . per ml. Most strains of *Staph. aureus* were inhibited by 1.0–2.0 μg . per ml. although a few strains required up to 12.5 μg . per ml. The gram-negative bacilli—including the typhoid bacillus and other members of the *Salmonella* group—were somewhat more resistant, their requirements ranging from 3.1 to 25.0 μg . per ml. Unfortunately, nearly all strains of *Proteus* and *Ps. aeruginosa* were found to be moderately or markedly resistant to the action of the drug (4.0 to 250 μg . per ml.) although, as shown by Rutenburg and Schweinburg,¹³ an occasional strain may be quite sensitive (0.0125 to 0.4 μg . per ml.). It is of considerable

theoretical and practical interest that some strains of Group D streptococci (*Str. faecalis*) are more sensitive *in vitro* to aureomycin than they are to penicillin.

Bryer et al.¹⁴ reported that strains of *Brucella suis* were completely inhibited *in vitro* by 0.25 to 0.5 μ g. of aureomycin per ml. and *Brucella abortus* by 0.25 to 2.0 μ g. per ml. Spink et al.¹⁵ also found that the drug was active against these species as well as *Brucella melitensis* both in the experimentally infected chick embryo and in the test tube.

Experiments by Steenken and Wolinsky¹⁶ on the tuberculostatic effect of the drug indicated that growth of a standard laboratory strain of *M. tuberculosis*, H37Rv, was inhibited by from 2.5 to 40.0 μ g. per ml. depending upon the type of fluid medium employed. But the drug failed to modify the course of tuberculous disease in guinea pigs even when given in maximally tolerated dosage.

Price et al.¹¹ and Chandler and Bliss⁸ first pointed out that in tests for bacterial sensitivity the turbidity end points move up during successive days of incubation. This indicates that the drug has primarily a bacteriostatic action although it is also bactericidal in higher concentrations and reflects the progressive deterioration of the antibiotic which was previously mentioned. The effect might also be caused by the emergence of drug-resistant organisms, as is seen so commonly with streptomycin; but these authors, as well as Paine et al.,¹² have demonstrated that resistance to aureomycin is rarely developed by bacteria exposed to aureomycin *in vitro* and that such resistance, when it appears, is usually of a low order. Moreover, no evidence has yet been obtained that resistant organisms elaborate an anti-aureomycin substance or "aureomycinase."

From the standpoint of contemplated therapy it is important to note that bacteria which have developed a marked resistance to either penicillin or streptomycin still retain their native susceptibility to the effects of aureomycin *in vitro*.

Experimental Studies in Vivo. The extensive studies which have been made of the therapeutic effects of aureomycin *in vivo* can be only briefly summarized here. In general the results with various bacterial agents conform quite well to what might be predicted from the *in vitro* tests just described. Bryer et al.¹⁷ reported, for example, that aureomycin would satisfactorily protect mice against 10,000 lethal doses of Group A hemolytic streptococci even when relatively small doses were administered either orally or parenterally. Murine infections with type 1 pneumococci could also be cured, provided larger doses of the drug were given, but little protection was obtained against *K. pneumoniae*. Little¹⁸ as well as Price et al.¹¹ found that aureomycin gave poor therapeutic results in mice infected with *E. typhosa* and other representatives of the *Salmonella* group; but the latter authors obtained a fairly good effect with a strain of *E. coli* which was sensitive *in vitro*.

In *Brucella abortus* infections of mice Heilman¹⁹ found that aureomycin was superior to chloromycetin but that treatment with a combination of aureomycin and dihydrostreptomycin gave the best results. Heilman²⁰ also reported that aureomycin was highly effective against *Borrelia novyi* (relapsing fever) and *Leptospira icterohemorrhagiae* (Weil's disease) in small animals.

Aureomycin was discovered very early to be an astounding curative agent for rickettsial infections in both animals and chick embryos. Wong and Cox²¹ showed that the rickettsiae of epidemic typhus, Rocky Mountain spotted fever, scrub typhus, Q fever and rickettsialpox were all extremely sensitive to the drug although, it is important to note, there was no direct effect upon these organisms *in vitro*. Relatively small doses of aureomycin permitted the survival of chick embryos given multiple lethal doses of these rickettsiae, while infections in mice or guinea pigs could be either aborted by early treatment or easily cured after they were clinically established. Anigstein et al.²² were equally successful in treating epidemic

typhus and Rocky Mountain spotted fever in guinea pigs. Both groups of investigators made the important observation that animals treated at the time of infection or shortly afterward often showed no residual immunity whereas animals treated later in the disease were usually resistant to challenge inoculation with the original organism. This phenomenon indicates that aureomycin—unlike para-aminobenzoic acid—has rickettsiocidal as well as rickettsiostatic properties.

Wong and Cox²¹ found aureomycin to have marked therapeutic activity in mice infected either intracerebrally or intraperitoneally with the viruses of psittacosis and lymphogranuloma venereum. Moreover, these viruses did not persist in surviving animals to the same extent as they customarily do when a sulfonamide drug such as sulfadiazine is used as the therapeutic agent. Aureomycin failed to show any therapeutic activity against the following viruses: influenza A and B, canine distemper, rabies, Newcastle disease, Venezuelan equine encephalomyelitis and the MEF-1 strain of poliomyelitis. Experiments with mumps virus in chick embryos showed that the drug reduced or completely inhibited the production of viral hemagglutinin but failed to modify the rate of multiplication or to reduce the infectivity of the virus. In our experience²³ aureomycin had no effect on the viruses of vaccinia and herpes simplex in either mice or chick embryos.

Absorption and Excretion in Man. Studies of the absorption and excretion of aureomycin have been handicapped by the lack of an accurate and uniform method of microbiologic assay of the antibiotic. Since the activity of the drug deteriorates more or less rapidly and irregularly *in vitro*, standard twenty-four-hour dilution series methods such as those used for the determination of penicillin will give variable and erroneous results. The method most widely accepted at present was developed by Dornbush and Pelcak⁷ and employs a strain of *B. cereus* as the test organism, with an incubation period of only four hours at 37°C.

Dowling and his associates^{24,25} measured the concentration of aureomycin in the blood, cerebrospinal fluid, urine and milk after giving doses of 0.1 to 1.0 Gm. orally and intramuscularly to adults or equivalent amounts to children. Low peak blood levels were found one hour after intramuscular injection of 0.1 Gm., averaging 0.4 $\mu\text{g.}$ per ml. and rapidly declining over the first six hours. When 0.7 or 1.0 Gm. of the drug was given by mouth the maximal blood levels were reached about six hours later and averaged 1.08 $\mu\text{g.}$ per ml. Aureomycin appeared rapidly in the urine in concentrations up to 128 $\mu\text{g.}$ per ml. from two to four hours after oral administration. Low levels ranging from 0.03 to 0.13 $\mu\text{g.}$ per ml. were found in the cerebrospinal fluid of six among nine patients; these levels corresponded to blood concentrations of 0.13 to 4.0 $\mu\text{g.}$ per ml. In one patient no aureomycin could be detected in the milk when the blood level was 2.0 $\mu\text{g.}$ per ml.

Finland and his colleagues^{26,27} found that plasma levels were usually about 2.0 $\mu\text{g.}$ per ml. following oral doses up to 1.0 Gm. every six hours. The maximal rate of excretion in the urine occurred from four to eight hours after ingestion when the concentration ranged as high as 256 $\mu\text{g.}$ per ml. The drug continued to be excreted for two or three days after a single dose of 0.5 or 0.75 Gm. and antibiotic activity equivalent to 12 or 15 per cent of a single oral dose could be recovered by the admittedly crude methods employed. Aureomycin could not be recovered from the bile during oral treatment although bile itself did not inhibit the drug *in vitro*.

Brainerd et al.²⁸ reported that the maximal serum concentration of aureomycin occurred from two to four hours after an initial dose of 1.0 Gm. by mouth, the levels ranging from 0.3 to 2.5 $\mu\text{g.}$ per ml. Cumulative effects were noted in most individuals who received the drug on a continuous schedule every four to six hours, with levels rising as high as 20 $\mu\text{g.}$ per ml. during a six-hour period. When doses of 0.05 Gm. were given intravenously the serum con-

centration rose sharply to between 0.6 and 5.0 $\mu\text{g.}$ per ml. within five minutes and then declined gradually during the next six hours. However, the intramuscular injection of 0.05 to 0.2 Gm. was rarely followed by measurable concentrations in the blood and a level exceeding 0.15 $\mu\text{g.}$ per ml. was observed only once in twenty-one determinations. These authors were unable to detect aureomycin in the cerebrospinal fluid of two adults who received single oral doses of 1.0 Gm. and in a child following the ingestion of 2.0 Gm. over a period of twenty-four hours.

The results of other studies by Schoenbach,²⁹ O'Leary,³⁰ Meads,³¹ Harrell³² and their associates are essentially in agreement with those given previously. It seems clear, therefore, that either the oral or the intravenous administration of aureomycin to human subjects may give blood concentrations within the therapeutic range for many bacteria, as judged by their *in vitro* sensitivities. Intramuscular injection would appear to be less satisfactory since the levels with comparable doses are lower and more erratic. Large amounts of active drug are excreted in the urine whatever the route of administration but relatively little enters the cerebrospinal fluid. However, it should be re-emphasized that current methods for the determination of aureomycin probably permit only a rough approximation in the laboratory of the activity and fate of the drug in the body.

Dosage and Mode of Administration in Man. Aureomycin hydrochloride is only moderately soluble and nearly 5 ml. of water or normal saline are required to dissolve 50 mg. of the drug. To inject such a volume of a strongly acid solution intramuscularly causes intense pain. Moreover, intravenous administration is also painful and the subsequent incidence of thrombophlebitis is high. These facts, together with the obvious drawbacks connected with repeated intravenous injections, have led to its use principally by mouth.

A variety of dosage schedules with the oral preparation have been described, the

amounts varying from 30 to 100 mg. per kg. and the intervals between doses anywhere from one to six hours. The antibiotic is now put up in 250 mg. capsules and it has been our habit to regard 4 Gm. per day (1 Gm. every six hours) as the "standard" dose for an acutely ill adult of average size. At times when the condition seemed critical we have increased this to 6 Gm. the first day. If the result of treatment is favorable this dose is reduced after two or three days to 2 Gm. or even lower. If nausea is a prominent feature smaller doses at shorter intervals may be given. The taking of milk, aluminum hydroxide gel, phenobarbital, etc., along with the drug has proved helpful. It is very uncommon to be compelled to discontinue treatment altogether on account of nausea.

For intramuscular injection 30 to 50 mg. of the drug in 3 to 5 ml. of fluid together with procaine may be given at six hourly intervals. As has been stated this is a painful proceeding and if buffers are employed to diminish the acidity it must be remembered that the antibiotic rapidly loses its potency in solution at a neutral or alkaline reaction. A new vehicle for its intravenous administration, L (—) leucine, has recently been introduced by the Lederle Laboratories. In 5 ml. of this diluent (containing 131 mg. of leucine) 100 mg. of aureomycin hydrochloride may be dissolved. This can be injected directly at a very slow rate or added to an infusion of isotonic dextrose or saline. As much as 400 or 500 mg. every twelve hours may be given to very seriously ill patients. On the whole, oral administration has obvious advantages.

CLINICAL USE OF AUREOMYCIN

Protozoal Diseases. McVay et al.³³ have recently reported rapid cures in fourteen cases of amebic colitis with aureomycin by mouth. Symptoms rapidly subsided and the stools became negative in a few days. Strains of amebae isolated from three of these were exposed to the drug *in vitro* and it was shown to have an amebicidal effect.

Diseases Due to Spirochetes. O'Leary and co-workers³⁰ reported two cases of acute

syphilis in which the patients were treated orally with aureomycin. Results generally comparable to what would be expected with penicillin were obtained.

Bacterial Diseases. Coccid Infections: Finland and his associates³⁴ treated four patients with pneumococcal pneumonia with aureomycin and reported results entirely similar to those obtained with penicillin. At this clinic we have had the same experience. The authors also described excellent results in one case of meningococcemia. In regard to sixty cases of gonococcal urethritis, however, their findings were different, and they concluded that although the drug was effective it was distinctly inferior to penicillin.²⁶ It may be remarked, however, that small doses were administered in many of these cases.

Schoenbach²⁹ and Ross³⁵ and their colleagues have reported the successful use of aureomycin in localized staphylococcal infections including two cases with positive blood cultures.

Bacillary Infections. Among the most brilliant effects of aureomycin are those recorded in the treatment of brucellosis. The first case was reported by Bryer et al.³⁶ who subsequently added four more cases.¹⁴ The strains involved were Br. abortus and Br. suis. A little later Spink and co-workers¹⁵ treated twenty-four patients with Br. melitensis infection. A recent report of the treatment of melitensis infection was made by Knight et al.³⁷ who described five additional cases. All of the cases were proven by blood cultures; some were of short duration, some had gone on for many months and some were critically ill. There was general agreement on the results obtained. In every instance the temperature became normal within two to five days after commencement of therapy. Blood cultures almost invariably became sterile quite promptly and the symptoms and signs of disease defervesced with equal speed. It is also to be remarked that relatively small total doses of drug were administered to these patients (1.0 to 2.0 Gm. daily) and that equally good results were recorded with

a variety of different treatment schedules. Spink reported an interesting Herxheimer-like reaction at the beginning of treatment in twelve of his twenty-four patients—an abrupt rise in temperature eight to twelve hours after the first dose of aureomycin, accompanied occasionally by symptoms of shock. He recommends a treatment period of eleven days, starting with small doses: 0.1 Gm. in divided doses the first day, 0.6 the second, 1.6 the third and 2.0 each day thereafter. Herrell and Barber³⁸ have reported excellent therapeutic results in four cases in which patients were treated simultaneously with 3.0 Gm. of aureomycin orally and 2.0 Gm. of dihydrostreptomycin intramuscularly each day for eleven to fifteen days.

Tularemia also responds very favorably to treatment with aureomycin. Woodward et al.³⁹ recorded its effect in three patients, one of whom was critically ill at the time treatment was begun. In all the response was prompt and striking, being quite as satisfactory as the best results with streptomycin.

In view of its antibacterial powers *in vitro* it is not surprising that aureomycin has been tried in a number of infections due to members of the colon-typhoid group. The first report by Bryer et al.³⁶ noted its effectiveness in two patients with infection of the urinary tract due to coli-aerogenes. Ten additional cases of urinary tract infection with a variety of organisms including A. aerogenes, E. coli, Proteus and Ps. aeruginosa, several of them mixed with S. viridans and S. fecalis, were reported cured by Rutenberg and Schweinburg.¹³ We have had a similar experience at our clinic but on the whole we have been unimpressed by the action of aureomycin in severe infections outside the urinary tract due to Ps. aeruginosa and Friedländer's bacillus in particular.

Disappointing experiences with typhoid fever and Salmonella infections have been reported by Collins et al.⁴⁰ We, too, have noted therapeutic failures with bacteria of the Salmonella group. McDermott et al.⁴¹

concluded that the efficacy of aureomycin in typhoid fever was very much less than that of chloromycetin.

Pulmonary Tuberculosis. Steinbach et al.^{41a} used aureomycin in the treatment of three young adult patients with extensive acute pulmonary tuberculosis. The drug was administered mostly by mouth in doses of 2.0 Gm. to 4.0 Gm. daily for periods of from thirty-four to ninety-four days. In each case the sputum remained positive for tubercle bacilli and the patient showed no improvement either clinically or by x-ray during the treatment period. All three patients had a prompt therapeutic response to streptomycin after aureomycin was discontinued.

Diseases Due to Rickettsiae. Laboratory studies having indicated a powerful anti-rickettsial action of aureomycin, it followed that some of the first clinical trials of the agent were in this group of diseases. Since chloromycetin had already been proven to be effective in scrub typhus, it was hoped that aureomycin would act similarly. On the whole these expectations have been abundantly justified. Aureomycin has been found to be consistently successful in the treatment of Rocky Mountain spotted fever by Bryer et al.,³⁶ Cooke,⁴² Ross et al.⁴³ and Harrell et al.;³² in Q fever by Lennette et al.;⁴ in Brill's disease by Schoenbach;⁴⁴ in typhus by Knight et al.;³⁷ and in rickettsial-pox by Rose.⁴⁵ Its action in all these various types of rickettsial infections has been remarkably uniform. Within twenty-four hours after the first dose there is an obvious change for the better in the patient's clinical condition. He appears brighter, "toxemia" seems less, the temperature is lower and there is welcome relief of headache. At the end of forty-eight hours in most instances the temperature has reached normal levels, where it remains, and convalescence proceeds uneventfully. At times this does not take place until the third day but in any case all observers concede that aureomycin interrupts the course of every rickettsial disease thus far studied in dramatic style. To judge from published reports it appears

fully as effective as chloromycetin and is much superior to para-aminobenzoic acid.

Diseases Due to Filterable Viruses. Evidence afforded by laboratory experiments warranted an early trial of aureomycin in lymphogranuloma venereum; this was accomplished by Wright et al.⁶ In their original paper, amplified by a second,⁴⁶ these authors have reported the results of treatment in thirty-five cases. Some of these patients had buboes, some acute proctitis and some rectal strictures. There was a remarkable and surprisingly prompt effect on the buboes. In a very few days they were materially shrunken and follow-up revealed that the remission was sustained. Acute proctitis responded equally well. The proctitis associated with rectal stricture also cleared although the chronic anatomic changes persisted. These authors, from the wealth of their experience in their disease, concluded that aureomycin surpassed any mode of therapy previously used.

All of the aforementioned clinical results with aureomycin might have been anticipated from the laboratory data existing at the time the drug was released for clinical investigation. The most unexpected finding in regard to this antibiotic was its curative effect in "primary atypical" or "virus" pneumonia, which was first reported by Kneeland et al.⁴⁷ and confirmed by Schoenbach and Bryer,⁴⁸ Finland et al.,⁴⁹ and Meiklejohn and Schragg.⁵⁰ The findings of all these groups have been essentially identical. Cases conforming to the accepted clinical pattern of atypical pneumonia, many of them with serologic confirmation of the diagnosis and most of them having been demonstrated to be unresponsive to penicillin, have almost without exception responded to aureomycin. In general the type of response resembles that seen in rickettsial diseases, particularly Q fever. That is to say, within eighteen to twenty-four hours there is a definite improvement in the patients' general clinical condition, with lessening of fever, cough, headache and "toxemia." Ordinarily the temperature reaches normal levels at the end of forty-

eight hours and convalescence proceeds smoothly. In our experience, if the treatment is stopped at this juncture a relapse will occur but this may again be brought under control by re-administration of the drug. Perhaps the most interesting aspect of these results is the implication that the agent causing primary atypical pneumonia may belong to the category of larger filterable viruses of the lymphogranuloma-pneumonia group.

Ocular Conditions. Braley and Sanders^{51,52} described the use of aureomycin mainly as a local application in the form of aureomycin borate, 0.5 per cent solution, in a wide variety of ocular infections. Excellent results were described in conjunctivitis due to staphylococcus, pneumococcus, *H. influenzae* and Morax-Axenfeld bacillus. Reports of several virus diseases of the conjunctiva and cornea were also included. The drug appeared effective in inclusion conjunctivitis and in one case of trachoma. It was also favorably reported in herpetic conjunctivitis although how this diagnosis was established is not stated. Only eight of twenty-seven patients with epidemic keratoconjunctivitis appeared to benefit from the treatment but the authors state that, even so, aureomycin was more effective than any other agent thus far studied.

Miscellaneous Conditions. Seven patients with granuloma inguinale have been treated orally with aureomycin and all of them showed a very satisfactory response according to Wright et al.⁴⁶ and Greenblatt et al.⁵³

In our own experience as well as in the hands of others aureomycin has had equivocal or negative effects in infective hepatitis and infectious mononucleosis. Although the evidence was not absolutely clear-cut we concluded that it was not effective in the common cold.⁵⁴ It has been tried in a number of conditions of undetermined etiology such as rheumatoid arthritis, Hodgkin's disease, periarteritis nodosa, lupus erythematosus disseminatus, ulcerative colitis and Guillain-Barré syndrome without beneficial results. Its action in herpes zoster

appears to be equivocal. In our experience herpes simplex is unaffected.

SUMMARY AND CONCLUSIONS

A general review of the literature on aureomycin, both biological and clinical, indicates that it is an important landmark in the field of antibiotics. Its extremely low toxicity, wide range of activity and absorbability from the gastrointestinal tract combine to make it a powerful therapeutic weapon. To an extraordinary degree it approximates in a single agent the aggregate effects of the sulfonamides, penicillin and streptomycin in addition to its antirickettsial and antiviral properties. Although the factor of expense still influences its widespread use it appears now to be the unquestioned agent of choice in brucellosis, lymphogranuloma venereum, primary atypical pneumonia and possibly granuloma inguinale. In addition it seems to have achieved a place in the treatment of ocular infections. In typhoid fever it would appear to be clearly inferior to chloromycetin. In other fields where chemotherapy and antibiotics have proved useful its versatility places it in the front rank.

REFERENCES

1. DUGGAR, B. M. Aureomycin: a product of the continuing search for new antibiotics. *Ann. New York Acad. Sc.*, 51: 177, 1948.
2. BROSHARD, R. W., DORNBUSH, A. C., GORDON, S., HUTCHINGS, B. L., KOHLER, A. R., KRUPKA, G., KUSHNER, S., LEFEMINE, D. V. and PIDACKS, C. Aureomycin, a new antibiotic. *Science*, 109: 199, 1949.
3. HARNED, B. K., CUNNINGHAM, R. W., CLARK, M. C., COSGROVE, R., HINE, C. H., MCCAULEY, W. J., STOKEY, E., VESSEY, R. E., YUDA, N. N. and SUBBAROW, Y. The pharmacology of duomycin. *Ann. New York Acad. Sc.*, 51: 182, 1948.
4. LENNETTE, E. H., MEIKLEJOHN, G. and THELEN, H. M. Treatment of Q fever in man with aureomycin. *Ann. New York Acad. Sc.*, 51: 331, 1948.
5. COLLINS, H. S., PAINE, T. F., JR. and FINLAND, M. Clinical studies with aurcomycin. *Ann. New York Acad. Sc.*, 51: 231, 1948.
6. WRIGHT, L. T., SANDERS, M., LOGAN, M. A., PRICOT, A. and HILL, L. M. Aureomycin: a new antibiotic with virucidal properties. I. A preliminary report on successful treatment in twenty-five cases of lymphogranuloma venereum. *J. A. M. A.*, 138: 408, 1948.

7. DORNBUSH, A. C. and PELCAK, E. J. The determination of aureomycin in serum and other body fluids. *Ann. New York Acad. Sc.*, 51: 218, 1948.
8. CHANDLER, C. A. and BLISS, E. A. In vitro studies with aureomycin. *Ann. New York Acad. Sc.*, 51: 221, 1948.
9. PAINE, T. F., JR., COLLINS, H. S. and FINLAND, M. Laboratory studies with aureomycin. *Ann. New York Acad. Sc.*, 51: 228, 1948.
10. BLISS, E. A. and CHANDLER, C. A. In vitro studies of aureomycin, a new antibiotic agent. *Proc. Soc. Exper. Biol. & Med.*, 69: 467, 1948.
11. PRICE, C. W., RANDALL, W. A. and WELCH, H. Bacteriological studies of aureomycin. *Ann. New York Acad. Sc.*, 51: 211, 1948.
12. PAINE, T. F., JR., COLLINS, H. S. and FINLAND, M. Bacteriologic studies on aureomycin. *J. Bact.*, 56: 489, 1948.
13. RUTENBURG, A. M. and SCHWEINBURG, F. B. Aureomycin in urinary infections due to gram negative organisms. *Proc. Soc. Exper. Biol. & Med.*, 70: 464, 1949.
14. BRYER, M. S., SCHOENBACH, E. B., WOOD, R. M. and LONG, P. H. The treatment of acute brucellosis with aureomycin. *Bull. Johns Hopkins Hosp.*, 84: 444, 1949.
15. SPINK, W. W., BRAUDE, A. I., CASTANEDA, M. R. and GOYTIA, R. S. Aureomycin therapy in human brucellosis due to *Brucella melitensis*. *J. A. M. A.*, 138: 1145, 1948.
16. STEENKEN, W. and WOLINSKY, E. Tuberculostatic activity of aureomycin in vitro and in vivo. *Am. Rev. Tuberc.*, 59: 221, 1949.
17. BRYER, M. S., SCHOENBACH, E. B., BLISS, E. A. and CHANDLER, C. A. Treatment of experimental infections with aureomycin. *Ann. New York Acad. Sc.*, 51: 254, 1948.
18. LITTLE, P. A. Use of aureomycin on some experimental infections in animals. *Ann. New York Acad. Sci.*, 51: 246, 1948.
19. HEILMAN, F. R. The effect of combined treatment with aureomycin and dihydrostreptomycin on *Brucella* infections in mice. *Proc. Staff Meet., Mayo Clin.*, 24: 133, 1949.
20. HEILMAN, F. R. Aureomycin in treatment of experimental relapsing fever and leptospirosis icterohemorrhagica (Weil's disease). *Proc. Staff Meet., Mayo Clin.*, 23: 569, 1948.
21. WONG, S. C. and COX, H. R. Action of aureomycin against experimental rickettsial and viral infections. *Ann. New York Acad. Sc.*, 51: 290, 1948.
22. ANIGSTEIN, L., WHITNEY, D. M. and BENINSON, J. Aureomycin—a new antibiotic with antirickettsial properties: its effect on experimental spotted fever and epidemic typhus. *Ann. New York Acad. Sc.*, 51: 306, 1948.
23. ROSE, H. M. Unpublished observations.
24. DOWLING, H. F., LEPPER, M. H., SWEET, L. K. and BRICKHOUSE, R. L. Studies on serum concentrations in humans and preliminary observations on the treatment of human infections with aureomycin. *Ann. New York Acad. Sc.*, 51: 241, 1948.
25. LEPPER, M. H., DOWLING, H. F., BRICKHOUSE, R. L. and CALDWELL, E. R., JR. Blood and cerebrospinal fluid concentrations of aureomycin after oral and intramuscular administration. *J. Lab. & Clin. Med.*, 34: 366, 1949.
26. FINLAND, M., COLLINS, H. S. and PAINE, T. F., JR. Aureomycin, a new antibiotic: results of laboratory studies and of clinical use in 100 cases of bacterial infections. *J. A. M. A.*, 138: 946, 1948.
27. COLLINS, H. S., WELLS, E. B., PAINE, T. F., JR. and FINLAND, M. Urinary excretion of aureomycin. *Proc. Soc. Exper. Biol. & Med.*, 69: 174, 1948.
28. BRAINERD, H. D., BRUYN, H. B., JR., MEIKLEJOHN, G. and SCAPARONE, M. Assay of aureomycin in body fluids: observations on individuals receiving aureomycin. *Proc. Soc. Exper. Biol. & Med.*, 70: 318, 1949.
29. SCHOENBACH, E. B., BRYER, M. S. and LONG, P. H. The pharmacology and clinical trial of aureomycin: a preliminary report. *Ann. New York Acad. Sc.*, 51: 267, 1948.
30. O'LEARY, P. A., KIERLAND, R. R. and HERRELL, W. E. Oral administration of aureomycin (duomycin) and its effect on *treponema pallidum* in man. *Proc. Staff Meet., Mayo Clin.*, 23: 574, 1948.
31. MEADS, M., HASLAM, N. M. and STEVENS, K. Aureomycin: in vitro observations on the antibacterial activity of a new antibiotic. *North Carolina M. J.*, 9: 568, 1948.
32. HARRELL, G. T., MEADS, M. and STEVENS, K. "Aureomycin": a new orally effective antibiotic. *South. M. J.*, 42: 4, 1949.
33. MCVAY, L. V., LAIRD, R. L. and SPRUNT, D. H. A preliminary report of the successful treatment of amebiasis with aureomycin. *Science*, 109: 590, 1949.
34. COLLINS, H. S., PAINE, T. F., JR. and FINLAND, M. Aureomycin in treatment of pneumococcal pneumonia and meningococcemia. *Proc. Soc. Exper. Biol. & Med.*, 69: 263, 1948.
35. ROSS, S., BURKE, F. G., RICE, E. C., SCHOENBACH, E. B., BISCHOFF, H. and WASHINGTON, J. A. Aureomycin; preliminary report of a clinical trial. *Clin. Proc. Child. Hosp.*, Washington, D. C. 4: 315, 1948.
36. BRYER, M. S., SCHOENBACH, E. B., CHANDLER, C. A., BLISS, E. A. and LONG, P. H. Aureomycin: experimental and clinical investigations. *J. A. M. A.*, 138: 117, 1948.
37. KNIGHT, V., RUIZ-SANCHEZ, F., RUIZ-SANCHEZ, A. and McDERMOTT, W. Aureomycin in typhus and brucellosis. *Am. J. Med.*, 6: 407, 1949.
38. HERRELL, W. E. and BARBER, T. E. The combined use of aureomycin and dihydrostreptomycin in the treatment of brucellosis. *Proc. Staff Meet., Mayo Clin.*, 24: 138, 1949.
39. WOODWARD, T. E., RABY, W. T., EPPES, W., HOLBROOK, W. A. and HIGHTOWER, J. A. Aureomycin in treatment of experimental and human tularemia. *J. A. M. A.*, 139: 830, 1949.
40. COLLINS, H. S., PAINE, T. F., JR., WELLS, E. B. and FINLAND, M. Aureomycin—a new antibiotic: evaluation of its effects in typhoid fever, severe *Salmonella* infections and in a case of colon bacillus bacteremia. *Ann. Int. Med.*, 29: 1077, 1948.
41. McDERMOTT, W., KNIGHT, V. and RUIZ-SANCHEZ, F. Antimicrobial therapy in typhoid fever. *Tr. A. Am. Physicians*, in press.
- 41a. STEINBACH, M. M., DOONEEF, A. S. and BUCHBERG, A. S. The use of aureomycin in pulmonary tuberculosis. *Am. Rev. Tuberc.*, 59: 624, 1949.

42. COOKE, C. Rocky Mountain spotted fever treated with aureomycin. *J. A. M. A.*, 138: 885, 1948.
43. ROSS, S., SCHOENBACH, E. B., BURKE, F. G., BRYER, M. S., RICE, E. C. and WASHINGTON, J. A. Aureomycin therapy of Rocky Mountain spotted fever. *J. A. M. A.*, 138: 1213, 1948.
44. SCHOENBACH, E. B. Aureomycin therapy of reerudescent epidemic typhus (Brill's disease). *J. A. M. A.*, 139: 450, 1949.
45. ROSE, H. M. The treatment of rickettsialpox with aureomycin. (To be published.)
46. WRIGHT, L. T., SANDERS, M., LOGAN, M. A., PRIGOT, A. and HILL, L. M. The treatment of lymphogranuloma venereum and granuloma inguinale in humans with aureomycin. *Ann. New York Acad. Sc.*, 51: 318, 1948.
47. KNEELAND, Y., JR., ROSE, H. M. and GIBSON, C. D. Aureomycin in the treatment of primary atypical pneumonia. *Am. J. Med.*, 6: 41, 1949.
48. SCHOENBACH, E. B. and BRYER, M. S. Treatment of primary atypical non-bacterial pneumonia with aureomycin. *J. A. M. A.*, 139: 275, 1949.
49. FINLAND, M., COLLINS, H. S. and WELLS, E. B. Aureomycin in the treatment of primary atypical pneumonia. *New England J. Med.*, 240: 241, 1949.
50. MEIKLEJOHN, G. and SHRAGG, R. I. Aureomycin in primary atypical pneumonia. *J. A. M. A.*, 140: 391, 1949.
51. BRALEY, A. E. and SANDERS, M. Aureomycin in ocular infections. *J. A. M. A.*, 138: 426, 1948.
52. BRALEY, A. E. and SANDERS, M. Aureomycin in ocular infections: a study of its spectrum. *Ann. New York Acad. Sc.*, 51: 280, 1948.
53. GREENBLATT, R. B., DIENST, R. B., CHEN, C. and WEST, R. Oral aureomycin in the therapy of streptomycin-resistant granuloma inguinale. *South. M. J.*, 41: 1121, 1948.
54. KNEELAND, Y., JR., ROSE, H. M., GIBSON, C. D. and LAMB, A. R., JR. Experiences with aureomycin in the treatment of respiratory virus infections in man. *Tr. A. Am. Physicians*, in press.

Clinico-pathologic Conference

Pneumonia, Skin Eruption, Thrombophlebitis and Azotemia*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. R., (History No. 166026), was a retired postal clerk, seventy-seven years of age, who entered the Barnes Hospital on November 27, 1948, because of a skin eruption associated with cough and fever. The patient was unable to give an accurate history and the information which was available was obtained from his daughter and from correspondence with the physician who had cared for him at home. The family history indicated that one brother had died of "heart trouble" and another of tuberculosis. The patient had no significant exposure, however, to the latter. One sister died of carcinoma. The patient's general health was good until he reached the age of forty-four when he experienced nervousness and loss of weight for which a thyroidectomy was performed. Similar symptoms returned three years later and a second thyroidectomy was done. The patient's symptoms were relieved and he then remained well until one and one-half years before entry when he developed pneumonia. He was treated with a sulfonamide and later with penicillin. During convalescence a red swollen area appeared on the right arm just above the elbow and gradually extended downward over the forearm. At the same time he developed pain in both calves and a red, swollen, cord-like band appeared over the right calf. Similar areas were noted over other parts of his body including the face and the left thumb; gradually all the lesions

cleared completely. Studies in a hospital in the patient's own community were said to have been negative; the nature of these procedures, however, was not known.

One month prior to entry the patient developed a severe upper respiratory infection with fever and malaise. He was treated symptomatically without relief and then sulfamerazine therapy orally was instituted. The patient was also given 1 cc. of a repository penicillin preparation three times during a six-day period. Although his general condition improved somewhat, red tender nodules appeared first on his right ankle and right tibia and later over the arms, forearms, left leg and foot. The nodules were said to have been strikingly similar to those which he had developed with his previous infection one and one-half years before. He had low-grade fever with occasional spikes and a persistent hacking cough. Moderate periorbital edema developed and then subsided. A blood count at that time was said to have shown "a marked hypochromic anemia and a moderate leukocytosis." Because the patient failed to improve, three weeks before coming to the Barnes Hospital he entered the hospital in his own community. Reports from that institution stated that his red cell count was 3,100,000 and the hemoglobin 68 per cent. The white blood cell and differential counts were normal. The skin nodules faded but spiking temperatures persisted. At the end of the second week in the hospital the pa-

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

tient began to have severe chills and his temperature reached elevations of 103°F. Thrombophlebitis involving the superficial veins in both forearms and in one leg was noted. The patient's condition became worse and following one particularly severe chill his temperature reached 105°F. He developed an urticarial eruption. Following a transfusion of 400 cc. of whole blood he was sent to the Barnes Hospital for further studies.

Physical examination on entry revealed a temperature of 39.2°C., pulse 136, respirations 24 and blood pressure 135/65. The patient was a well developed but poorly nourished, lethargic, obtunded man who was acutely ill. Over the entire skin surface there were many red, raised lesions varying from 2 to 10 cm. in diameter; these were nodular and in some areas circinate with a raised border tending to clear from the center. In addition a number of small urticarial wheals were seen. The skin was hot and dry. Questionable swelling and pain on motion of some of the joints were noted. Many discrete, firm, non-tender, freely movable lymph nodes were palpable in the cervical, axillary and inguinal regions. The eyelids were reddened and rather swollen. The fundi revealed narrowing and tortuosity of the arterioles. No hemorrhages or exudates were seen. Hearing was obviously impaired. The nasal mucosa was red and partial bilateral obstruction was described. The pharynx was injected. The thyroid was not palpable. Signs of emphysema were present and there was slight dullness to percussion at the right base. Decreased breath sounds were noted at both bases posteriorly and in these areas moist sticky rales were heard. The heart was not enlarged. The rate was rapid but the sounds were of good quality. A grade 1 to 2 apical systolic blow was heard. The peripheral arteries were tortuous; those of the feet pulsated. Examination of the abdomen was entirely negative. The prostate was slightly enlarged. Two plus pitting edema of the ankles was present and there was slight swelling of the proximal pharyn-

geal joints and of the wrists, and some discomfort on flexion of the knees. Neurologic examination was essentially normal.

Laboratory findings were as follows: Blood count: red cells, 2,850,000; hemoglobin, 9 Gm.; white cells, 7,300; differential count: eosinophiles, 1 per cent; stab forms, 4 per cent; segmental forms, 78 per cent; lymphocytes, 14 per cent and monocytes, 3 per cent; platelet count, normal. Urinalysis: albumin, 1 plus; sugar, negative; sediment, showers of granular casts and occasional red cells. Stool examination: guaiac, negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 42 mg. per cent; total proteins, 6.8 Gm. per cent; albumin, 3.2 Gm. per cent; globulin, 3.6 Gm. per cent; cephalin-cholesterol flocculation test, 2+; thymol turbidity test, 13.8 units; total bilirubin, 0.86 mg. per cent; prothrombin time, 62.5 per cent of normal; sulfonamide level, 0. Blood cultures: no growth. Sedimentation rate: 1.3 mm. per minute (corrected). Sputum smear: no acid fast organisms seen. Sputum culture: coliform bacilli. Agglutination tests: typhoid, paratyphoid, OX-19 and brucella, all negative. Venous pressure: 80 mm. of sodium chloride. Circulation time (decholin): 12 seconds. Electrocardiogram: occasional auricular premature contraction. Roentgenograms of the chest: "There is peribronchial infiltration in the posterior portions of both lower lobes with no definite evidence of pneumonia."

Shortly after his entrance into the hospital the patient was seen in consultation by a dermatologist who made a diagnosis of erythema multiforme and urticaria. The patient was placed on a regimen which included 100,000 units of penicillin every three hours, a soft diet and supplementary vitamins. He also was given a blood transfusion after which his red cell count rose to 3,070,000 and the hemoglobin to 10.8 Gm. The patient continued to cough up a moderate amount of mucopurulent sputum and rales continued to be audible at both bases.

During his second hospital week he re-

remained rather obtunded. Because of the persistence of rales in the chest another x-ray was taken. This film revealed a great increase in the lung markings bilaterally. A third film taken several days later showed a minimum pleural effusion on the left. Intravenous pyelograms were essentially negative. Gastrointestinal roentgenograms were indeterminate. When the pleural effusion was demonstrated by x-ray examination a thoracentesis was done and 20 cc. of cloudy, light yellow fluid were removed. The fluid had a specific gravity of 1.018 and contained 3.6 Gm. per cent of protein. The fluid contained 2,700 cells with acid of which 76 per cent were polymorphonuclear forms. Culture of the fluid was negative. Repeated urinalyses revealed albuminuria and the sediment showed casts and occasional red cells.

During the first ten days of hospitalization the patient's temperature spiked each day to a maximum of 39.6°C.; on a single day two spikes were recorded. The pulse remained quite elevated. About the eleventh day this patient's temperature receded somewhat but for the following eight days was still slightly elevated. Basal rales persisted and on the eighteenth hospital day the patient coughed up blood-tinged sputum. Bleeding and clotting times were normal but the prothrombin time was 30 per cent of normal. Thrombophlebitis of the veins of the arms and legs became evident and edema of the lower extremities increased markedly. The patient was given amigen daily and more blood transfusions. The skin lesions of erythema multiforme and urticaria varied in intensity but after the administration of amigen became more prominent.

Skin and muscle biopsies were taken and microscopic examination of the sections revealed areas of acute and chronic inflammation of the muscle. The inflammatory cells consisted of polymorphonuclear leukocytes, mononuclear cells and a fair number of eosinophiles. There were no necrotizing lesions of the arterial walls. The dermis revealed very prominent acute and chronic

inflammatory changes and large masses of inflammatory cells. A diagnosis of acute and chronic inflammation of the skin and muscles, etiology undetermined, was made.

On the twentieth hospital day the patient again began to have spiking fever which reached 40°C. and continued for four days. Streptomycin therapy was then instituted. During this period of high fever sputum cultures revealed *Neisseria* and non-hemolytic streptococci. Smears of the sputum, however, also showed gram-negative rods. Physical examination revealed persistent rales at both lung bases.

The patient developed purpuric spots about the eyes and over the arms and trunk. Blood studies by the Hematology Department revealed the following: red cells, 2,970,000; hemoglobin, 10.2 Gm.; white cells, 13,050; platelets, 100,000; reticulocytes, 2.4 per cent; differential count: basophiles, 2 per cent; stab forms, 20 per cent; segmented forms, 73 per cent; lymphocytes, 4 per cent (three of which appeared young) and 1 monocyte. Toxic granules were seen in the polymorphonuclear leukocytes. Coagulation time, 4½ minutes; prothrombin time, 20 seconds; (normal control, 20 seconds); bleeding time, 22 minutes; clot retraction, poor. A diagnosis of thrombocytopenic purpura, probably secondary, was made. Several days later a repeat platelet count was 36,000. The patient exhibited increased difficulty in breathing and oxygen therapy became necessary. Gradually he became weaker although once again he was afebrile. During the last two weeks of life the urinary output on several days was markedly reduced and albuminuria at times was extremely pronounced. Near the end of his hospital course the total proteins were 5.5 Gm. per cent with albumin, 2.1 Gm. per cent and globulin, 3.4 Gm. per cent. The cephalin-cholesterol flocculation test remained at 4 plus and the thymol turbidity was 18.5 units. The non-protein was 38 mg. per cent and the white count had risen to 17,800. On December 25, 1948, the patient's temperature again spiked to 40°C. and he expired.

CLINICAL DISCUSSION

DR. W. BARRY WOOD, JR.: We all will agree that this patient presented an extremely complicated diagnostic problem. From the data available a number of organs which probably were involved by this disease process can be listed: first of all, the skin as indicated by erythema multiforme and urticaria; second, the blood vessels, particularly the veins, as evidenced by the fact that the patient had multiple thrombophlebitis; third, the patient had pain on motion in some of the joints; fourth, moderate lymphadenopathy was recorded. The lungs were the site of abnormal changes and the pleura may also have been primarily affected. The results of the surgical biopsy suggest that the muscle was pathologically involved and finally the anemia and thrombocytopenia suggest changes in the bone marrow involvement. One cannot be certain, however, that the changes in the blood were not secondary rather than primary. Dr. Moore, would you comment on the evidence which suggests that the liver also may have been incriminated?

DR. CARL V. MOORE: The liver function tests were certainly abnormal. Several tests were done and since all the results showed definite deviation from the normal I think one can be quite certain that the liver, like many other organs, was involved.

DR. WOOD: In the face of infection with high fever, such as was present in this case, can one rely on liver function tests to determine whether there is really organic disease damage in the liver itself?

DR. MOORE: I do not believe that an abnormal cephalin-cholesterol flocculation test *per se* would enable one to state that a patient had primary liver disease, but I doubt that the prothrombin time would be altered to the degree that it was here unless there was intrinsic hepatic disease.

DR. WOOD: Would you agree with that, Dr. Shank?

DR. ROBERT E. SHANK: Yes, I would. I believe that the liver can definitely be incriminated.

DR. WOOD: I should like to ask the students to suggest diagnoses which might explain all of the clinical manifestations exhibited by this patient.

STUDENT: Leukemia or lymphoma must be considered.

STUDENT: Polyarteritis nodosa may give rise to this type of clinical picture.

STUDENT: Stevens-Johnson's disease, so-called erythema multiforme exudativum, is characterized by certain features which were recorded here.

STUDENT: Disseminated lupus erythematosus.

DR. WOOD: That diagnosis is less likely here, of course, than it would be had this patient been a woman.

STUDENT: Dermatomyositis.

DR. WOOD: Does anyone care to suggest scleroderma? Certainly all of the collagen diseases must be discussed. Are there any other suggestions?

STUDENT: Buerger's disease should be mentioned in view of the venous involvement but I doubt that it could have caused the entire clinical picture.

DR. WOOD: We now have a considerable number of diagnostic possibilities and we shall attempt to evaluate them in the light of this patient's history and course in order to reach the correct diagnosis. Dr. Taussig, would you comment on the likelihood of leukemia having been the primary disease?

DR. BARRETT L. TAUSSIG: Considering the organs involved in this case, one by one, leukemia may indeed affect the skin and erythema nodosa may occur. Urticaria is certainly not common, however. Thrombophlebitis may be an accompanying complication of any disease process although I do not believe it is particularly common in leukemia. Similarly, the joints are not usually involved unless there is hemorrhage into a joint space. Lymph node enlargement, of course, is common although I would have expected perhaps even more adenopathy than was present in this instance. Although leukemic infiltration in the lungs is reported, I do not think the sequence of events here was particularly

characteristic; pleural involvement is not common. The kidneys and the muscle may be infiltrated with leukemic cells but again I think the changes seen here were rather marked for the usual findings in leukemia. Bone marrow changes, insofar as the red blood cells and the platelets are concerned, are entirely consistent. Considering the situation as a whole, I believe that the findings are not too much in favor of leukemia.

DR. WOOD: Dr. Sale, do you think lymphoma should be considered?

DR. LLEWELLYN SALE, JR.: Although many of the organs which were apparently involved in this instance may be affected in lymphoma, I believe that it is no more likely than is leukemia.

DR. WOOD: Let us inquire whether the hematologists will defend either of these diagnoses.

DR. MOORE: In view of the fact that the skin and muscle biopsy showed chronic inflammatory changes with infiltration of polymorphonuclear leukocytes, I think lymphoma can be ruled out; in lymphoma such infiltration is due to lymphocytic cells.

DR. WOOD: Dr. Goldman, do you think that the clinical picture is compatible with Boeck's sarcoid?

DR. ALFRED GOLDMAN: Neither the skin lesions nor the muscle biopsy findings are characteristic. The pulmonary manifestations, likewise, are not those usually seen in sarcoid although sarcoid may exhibit bizarre patterns in the lungs. Usually, however, the hilar lymph nodes are prominent; and if the process is widespread, miliary infiltration in both lungs is seen. I believe I would reject the diagnosis of sarcoidosis.

DR. WOOD: What is your feeling in regard to Stevens-Johnson's disease, Dr. Scott?

DR. VIRGIL C. SCOTT: Stevens-Johnson's disease, the etiology of which is not known, is manifested chiefly by fever, the lesions of erythema multiforme, particularly of the upper extremities, often with involvement of the pleural cavity and of the genitalia

and with skin lesions which are frequently vesicular and bullous. These bullae may rupture and may become secondarily infected. I do not think that this man had Stevens-Johnson's disease.

DR. WOOD: The skin manifestations might be explained on that basis and it is true that pneumonia may occur as a complication. In that regard there is an interesting report from Dr. Finland's laboratory in Boston reporting fatal cases of pneumonia in association with this syndrome.* However, I agree that that diagnosis does not explain all of the findings here and I believe that we can therefore eliminate it from further differential diagnosis. Dr. Smith, what about Buerger's disease?

DR. JOHN R. SMITH: It is quite unlikely that Buerger's disease could have been responsible for all of this man's difficulties. Thromboangitis obliterans when extensive may involve the vessels of all the extremities; it may affect the coronary arteries, cerebral arteries and indeed arteries to any organ. Usually, however, the site of the pathologic process is in the vessels of the legs, parallel involvement of both veins and arteries being common. I doubt that it needs serious consideration in this instance.

DR. WOOD: I would agree that it would be difficult to attribute all of the manifestations in this case to Buerger's disease. We are then left with diseases that are often classified together as diseases of the connective tissue or so-called collagen disease. The latter term is now widely used in the current literature and I think it would be well to discuss these possibilities in detail. Dr. Hampton, do you believe that the findings here are compatible with the diagnosis of polyarteritis nodosa?

DR. STANLEY F. HAMPTON: I think that that diagnosis seems most likely when one reads the protocol; I believe that it would explain the entire clinical picture.

DR. WOOD: In other words, the first diagnosis which would come to your mind,

* FINLAND, M., JOLLIFFE, L. S. and PARKER, F., JR. Pneumonia and erythema multiforme exudativum. *Am. J. Med.*, 4: 473, 1948.

having considered this protocol, would be polyarteritis nodosa. That impression is afforded support by the fact that when this patient had pneumonia, approximately one and one-half years before his final illness, he was given a sulfonamide and after recovery was fairly well until one month before admission when he acquired another respiratory infection and again was given a sulfonamide. Polyarteritis due to sulfonamide hypersensitivity is, of course, a now well known entity and one must therefore consider it seriously in this situation. Dr. Bukantz, do you agree that this patient definitely had polyarteritis nodosa?

DR. SAMUEL C. BUKANTZ: I have some doubt. I agree that most of the findings are extremely typical of polyarteritis with the possible exception of liver involvement. Some changes in liver function may be associated with polyarteritis but I am not aware of them.

DR. WOOD: Polyarteritis may, of course, involve vessels anywhere in the body and thus any organ. I believe the liver may be involved in a significant number of cases and therefore think that the hepatic abnormalities here do not necessarily exclude the diagnosis. What is your view on that subject, Dr. Hampton?

DR. HAMPTON: I agree with you.

DR. WOOD: What about venous involvement in periarteritis?

DR. KEITH S. WILSON: The veins may be involved in the disease. The bone marrow findings disturb me somewhat; I am not sure that they can be explained on the basis of polyarteritis. Perhaps the same drug sensitivity which gave rise to that entity, however, also exerted a toxic effect on the marrow.

DR. WOOD: Let us ask Dr. Moore whether he believes the bone marrow is involved primarily or secondarily here.

DR. MOORE: I do not know. There was no bone marrow aspiration performed on this patient, but I think that there is a definite possibility that the bone marrow involvement was primary for I have seen one other case in which thrombocytopenia

occurred in proven polyarteritis nodosa. The bone marrow changes may have been a manifestation of hypersplenism; that is, the spleen may have been involved primarily by polyarteritis and secondarily affected the bone marrow. I do not believe here that these two possibilities can be differentiated. Probably, even if a bone marrow aspiration had been done, the answer to that question could not be determined.

DR. WOOD: I am quite certain that the bone marrow was involved here. I do not think, however, that the clinical manifestations of bone marrow involvement are very common.

DR. WILSON: I think it is much more likely for drug sensitivity *per se* to produce bone marrow changes such as occurred here than for polyarteritis to do so. In addition, I believe that carcinoma of the pancreas should be considered.

DR. WOOD: Multiple venous thromboses occur not uncommonly in carcinoma of the body or tail of the pancreas and therefore that diagnosis should be mentioned. Multiple venous thromboses may occur with other carcinomas, too, may they not, Dr. Scheff?

DR. HAROLD SCHEFF: They may be seen with carcinoma anywhere in the body but are most often associated with carcinoma of the body or the tail of the pancreas.

DR. WOOD: Would you like to suggest, Dr. Wilson, that the entire clinical picture may be explained on the basis of carcinoma of the pancreas?

DR. WILSON: No, I think that the patient had polyarteritis also. However, urticaria and erythema multiforme may be seen as a concomitant of metastatic tumor from any primary source; it is particularly apt to occur if the liver is involved.

DR. WOOD: In other words, skin rashes may develop when the liver is involved by carcinoma.

DR. WILSON: Yes. It would be difficult, however, on the basis of pancreatic carcinoma to explain involvement of the kidney and of the muscles and therefore carcinoma of the pancreas is my second

choice; I do believe that it should be mentioned. As I have said before, I believe that the patient definitely had polyarteritis.

DR. WOOD: It appears that all the members of the allergy division made a single diagnosis; namely, that of polyarteritis nodosa.

DR. GOLDMAN: Does the absence of hypertension disturb any of the allergists in making that diagnosis?

DR. WILSON: There are a number of recorded cases of polyarteritis without renal involvement and those cases do not exhibit hypertension. It is true that approximately 75 per cent of the patients whose kidneys are the site of polyarteritis do develop hypertension.

DR. WOOD: Dr. Goldman, do you have any further comment?

DR. GOLDMAN: Recently Dr. George Baehr was here and discussed the collagen diseases. He made the statement that in the absence of hypertension one of the other collagen diseases should receive primary consideration.

DR. WOOD: Would you want to throw out the diagnosis of polyarteritis on the basis of Dr. Baehr's statement?

DR. GOLDMAN: Not entirely, but I would like to consider other collagen diseases.

DR. BUKANTZ: This discussion brings up a very important point. Classical polyarteritis nodosa is generally associated with hypertension and with lesions of the larger sized arteries; not infrequently occlusion occurs but such cases show no evidence of venous involvement. On this basis some pathologists have raised a question concerning the significance of the experimental form of polyarteritis which has been produced in rabbits, for many of the animals have shown not only arterial lesions but venous lesions as well. The type of diffuse vascular involvement, however, which is associated with hypersensitivity, such as to sulfonamide drugs, is characterized by widespread involvement of the smaller blood vessels. It is this type of vasculitis which resembles the experimental disease produced in rabbits by massive injections

of protein. This latter entity is often called polyarteritis nodosa although, as pointed out, it differs from the classical form.

DR. ROBERT J. GLASER: In view of this discussion of venous involvement, I believe a syndrome which is called migratory thrombophlebitis might be discussed. This clinical entity, which is not the one associated with carcinoma of the pancreas or of other organs but rather is associated with rheumatic fever, fits the clinical picture described here quite well. I have seen migratory thrombophlebitis only once and then in a rather young patient who had definite acute rheumatic fever. It has, however, been described by a number of writers and presumably is due to hypersensitivity. As has been noted, this patient also had erythema nodosa which, likewise, is assumed to be a manifestation of hypersensitivity. It seems to me, as Dr. Bukantz has clearly stated, that there is a whole group of diseases characterized by hypersensitivity, particularly to the sulfonamides which are not, at least by pathologists, called polyarteritis. Rather they are simply classified as having been due to sulfonamide hypersensitivity; they may be characterized by vascular involvement of almost any organ.

DR. WOOD: I think the terminology is not as important as an understanding of the general pathogenesis of this group of diseases; actually the term "collagen disease" which is now being used with increasing frequency includes all of these disease entities in one group and yet avoids the argument which Dr. Bukantz and Dr. Glaser have just raised, stressing the minor differences among them. In passing, I should like to ask if anyone would like to support the diagnoses of either lupus erythematosus disseminata or dermatomyositis.

STUDENT: Dr. Wood, in view of the fact that the biopsy of the skin and muscles did not show necrosis of the arterial walls but definite infiltration of the skin and muscles, would not one be more justified in making a diagnosis of dermatomyositis?

DR. WOOD: I believe that changes noted in the skin biopsy could go along with any of the diagnoses. Their differentiation is a matter of degree and may be most difficult. In summary, I believe it is fair to say that of all the suggestions made by the students, the staff is most enthusiastic about the group of collagen diseases. We have had some difficulty in defining which of the collagen diseases best fits this picture but we lean toward polyarteritis as being most likely. In view of the muscle involvement we realize that the pathologists may make a diagnosis of dermatomyositis; and if such is the case, the clinicians will not be disappointed.

DR. JOSEPH C. EDWARDS: Those of us who observed this patient during his lifetime believed that this was some form of collagen disease although we were not able to distinguish the exact form. The physician who referred the patient to this hospital suggested the possibility of sulfonamide hypersensitivity and also raised the question as to whether penicillin could have been responsible for this entity.

DR. WOOD: I do not recall any of the reports from the literature of proven polyarteritis nodosa following penicillin. Skin sensitivity to penicillin, of course, is well known but I do not believe that full blown polyarteritis has yet been described.

Clinical Diagnoses: Diffuse collagen disease, probably polyarteritis nodosa; ? carcinoma of the pancreas.

PATHOLOGIC DISCUSSION

DR. ANCEL EARP: There was pitting edema of the subcutaneous tissue of the feet and over the skin of the entire body there were numerous irregular purple or blue-black, non-elevated discolorations 0.5 to 5 cm. in diameter. The lungs were attached to the parietal pleura and diaphragm by loose fibrous adhesions and similar adhesions obliterated the interlobar fissures. The right pleural cavity contained approximately 100 cc. and the left 200 cc. of cloudy yellow fluid. The lungs together weighed 3,550 Gm. and were of a uniform fleshy

appearance and firm consistency. The cut surfaces bulged slightly and were gray and mottled with irregular red areas. The tissue was smooth and slightly translucent. A moderate amount of brownish red fluid oozed from the cut surfaces; the bronchi contained similar fluid. No gross abnormalities of the pulmonary vessels were noted.

The heart weighed 400 Gm. and in the epicardium there were many punctate ecchymoses. The abdominal cavity contained no free fluid. The right kidney weighed 205 Gm. and the left 180 Gm. The organs were pale and softer than normal. The capsules stripped with ease and finely granular surfaces with occasional flat-based irregular scars $\frac{1}{2}$ to 1 cm. in diameter were exposed. The cut surfaces of the cortex were pale and bulged slightly but the normal markings were easily discernible. Numerous punctate ecchymoses were present in the mucosa of the pelves and ureters. The spleen was moderately hyperplastic. The liver and biliary tract were of grossly normal appearance. Examination of the gastrointestinal tract revealed only focal areas of congestion in the mucosa. The wall of the urinary bladder was moderately trabeculated and the prostate was slightly enlarged.

DR. ROBERT A. MOORE: The dominant gross finding was a peculiar type of pneumonia which involved all lobes in a uniform rather than nodular manner and resulted in a fleshy, reddish gray appearance. It was associated with finely organized adhesions over the pleural surfaces and with pleurisy in the spaces between the adhesions. Except for the enlarged, soft kidneys, the other organs were not grossly remarkable and abnormal change consisted essentially of the presence of petechiae and ecchymoses. Our attention was therefore focused on the problem of the pneumonia.

Microscopically, the picture in the lung varied a good deal from low-power field to low-power field although the sections from all lobes of the lungs were essentially similar. In the region illustrated in Figure 1 the alveolar walls are thickened and enlarged

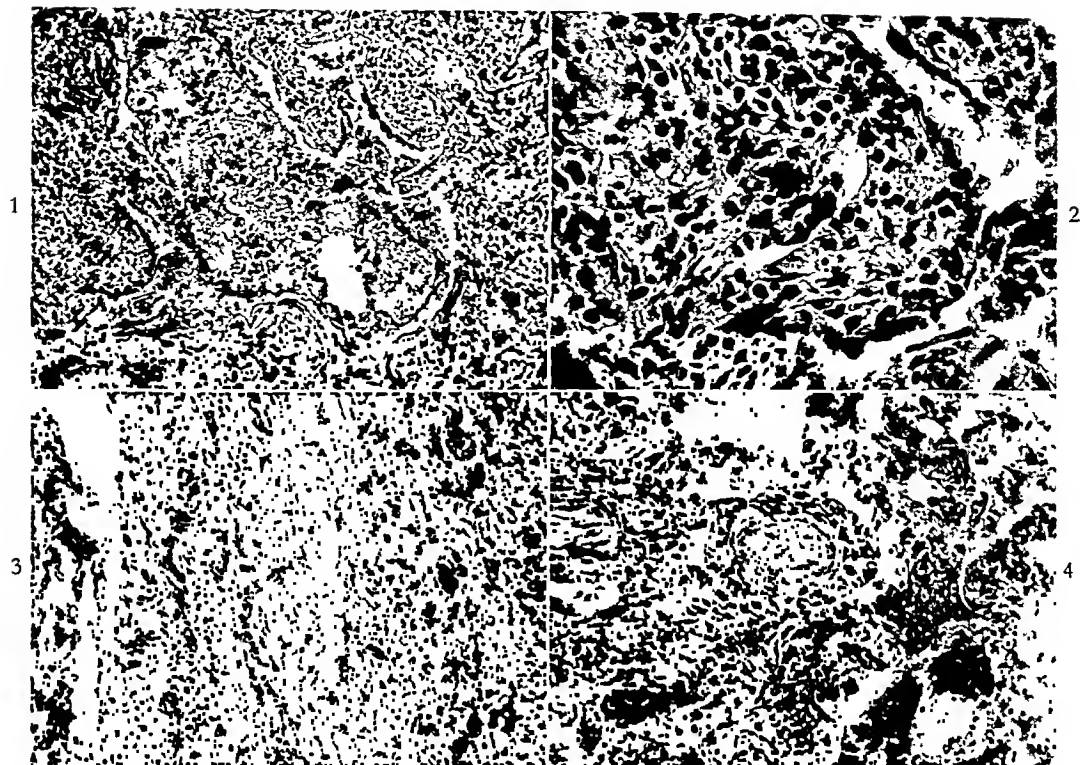


FIG. 1. Pneumonia of an unusual type characterized by a mononuclear infiltration, fibroblastic proliferation in the alveolar walls, metaplasia of the alveolar lining and cells, fibrin and precipitated protein in the alveoli.

FIG. 2. A more detailed view of the fibrous thickening and cellular infiltration of the alveolar walls of the lung and of the cuboidal cells lining the alveoli.

FIG. 3. An interlobular septum of the lung in which there is marked edema, fibrin and a mononuclear infiltration.

FIG. 4. Mononuclear infiltrate in the adventitia of a small artery in the lung without changes in the inner layers.

and the vessels are congested. In some alveoli there are large amounts of granular debris, some fibrin, large cells of the mononuclear type and a few polymorphonuclear leukocytes. The definite increase in thickness of the alveolar walls resulted not only from infiltration with fluid but also from the proliferation of fibroblasts and the infiltration of cells, most of which were lymphocytes and mononuclear cells. Some of the mononuclear cells were in the alveolar lumens and appeared as pulmonary phagocytes. In Figure 2 there is a more detailed view of the alveolar walls with an alveolus which was lined by cuboidal cells. The alveolar wall contains a rather robust fibroblastic stroma infiltrated with cells of the mononuclear and lymphocytic series.

Bacteriologic cultures of the lung revealed a few colonies each of staphylococci, diph-

theroids and a *Klebsiella* organism, but none of these organisms was present in sufficient numbers to indicate that it was responsible for such advanced disease. Bacterial stains of sections of the lung confirmed the impression that these organisms were etiologically not significant, for bacteria could not be identified in either the regions where there were polymorphonuclear leukocytes or mononuclear cells, or in the interstitial tissue or alveoli. Because of the interstitial fibrotic reaction which we thought might have been related to the clinical history of two episodes of pneumonia and because of the presence of myocarditis and interstitial nephritis, as will be described, the possibility of rickettsiae as the etiologic agent was considered but special stains for such organisms were negative. This pneumonia, therefore, can-

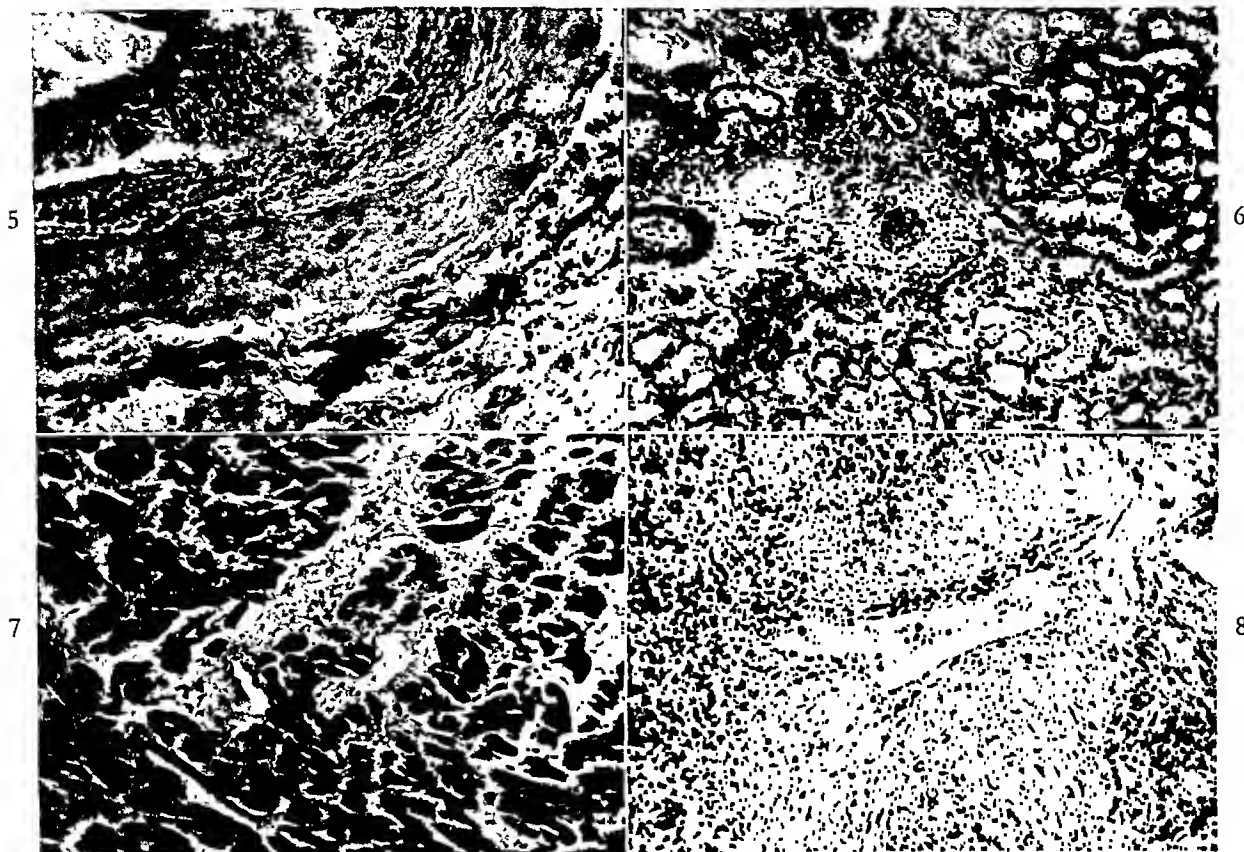


FIG. 5. Sub-intimal mononuclear infiltration of a moderate sized branch of the pulmonary artery without changes in the media or adventitia.

FIG. 6. A focal lesion in the cortex of the kidney about a small necrotic artery which is quite similar to the vascular lesion of disseminated lupus erythematosus.

FIG. 7. Myocarditis composed of an interstitial infiltrate of mononuclear cells.

FIG. 8. Sub-intimal mononuclear infiltration of a vein in the spleen similar to the lesions in larger pulmonary arteries and veins throughout the body.

not be established as having been due to a specific organism.

This peculiar type of pneumonia was characterized by early fibrous organization of interstitial inflammation, co-existent with exudation of leukocytes and mononuclear cells into the alveoli. Further, as illustrated in Figure 3, in the interlobular septa there is tremendous edema and distention of the lymphatic spaces with very slight infiltration of mononuclear cells. Around some of the small blood vessels in the lungs (Fig. 4) there is a definite perivascular cellular infiltrate composed of mononuclear cells with a few lymphocytes. No eosinophilic or neutrophilic leukocytes are present and, so far as we can determine, there is no swelling or fibrinoid change of the collagen. In the intima of some of the blood vessels of the lung, such as the moderate sized branch of the pulmonary artery seen in Figure 5, there is thickening and cellular infiltration

of the intima with the same types of cells present in the other infiltrates. In the adventitia and media there are no significant changes.

In the sections of the kidney there were numerous focal lesions in the cortex characterized by separation of the tissue, edema and cellular infiltration with the same types of mononuclear cells, and in the particular instance illustrated (Fig. 6) one of the foci includes a small artery which is definitely necrotic and appears to have been previously swollen by edema and infiltrated by mononuclear cells. In the myocardium (Fig. 7) there are no vascular lesions, but in a few foci increased numbers of mononuclear cells in the interstitial tissue are seen. These cells resemble those of the infiltrates in the other organs and are not the so-called Antischkow myocytes seen in many non-specific inflammations of the myocardium.

An example of a lesion present in many veins is seen in Figure 8 taken from the spleen; throughout the body changes similar to those in the pulmonary arteries are noted in that the endothelium is lifted off the vessel wall and mononuclear cells have infiltrated beneath the endothelium. This lesion is non-specific and is seen throughout the body in a wide variety of diseases.

In sections of the liver there was very definite but slight cirrhosis. There were no vascular lesions in the liver, however, and no cellular infiltration of any significance.

It is our conclusion that the lesion in the lung is to some extent suggestive of the type which occurs in hypersensitivity reactions, but it cannot be explained entirely on that basis. There was something additional in the nature of an interstitial and exudative pneumonia with organization which is not, so far as we are aware, consistent with what has been described and with what we have observed in reactions to the sulfonamide drugs or other sensitizing agents *per se*. On the other hand, the very definite lesions in the kidney cannot be explained on the same basis as the pneumonia. Furthermore, in the biopsy specimen of the muscle there was very definite interstitial myositis with polymorphonuclear leukocytes, and in the myocardium at autopsy there was a focal but definite interstitial myocarditis. The only interpretation of this case that I can offer to fit the clinical and pathologic observations would be as follows:

This patient had pneumonia about one and one-half years before death treated with one of the sulfonamide drugs. Over a year later he again developed pneumonia, the cause of which we cannot demonstrate. He was again treated with sulfonamides and at the time he died was apparently suffering from two diseases, pneumonia of unknown causation and a sensitivity reaction to

sulfonamides, manifest in the heart, kidneys and veins throughout the body.

It is a perplexing problem to choose a name for the disease I have described. This patient did not have the lesions of the classical type of polyarteritis nodosa in which there are changes in the adventitia and media of the arteries as well as in the intima, nor were the changes those of dermatomyositis. The artery in the section from the kidney could pass for an artery from a case of disseminated lupus erythematosus, but changes in more than one artery are necessary in order to make that diagnosis. It has, however, become the consensus in the literature in the last few years, and it has certainly been our experience, that these diseases are not the distinct entities pathologically that they were once thought to be; rather they represent expressions of a diffuse disease of collagen which may take different forms in different patients or even in the various organs of a single patient. I believe that this patient did have a sensitivity type of reaction, evidenced by diffuse disease of the collagen, but that in addition he developed pneumonia of some peculiar type which apparently marked the beginning of the terminal episode.

Final Anatomic Diagnosis: Atypical pneumonia of all lobes of the lungs; non-suppurative interstitial nephritis; interstitial myocarditis; sub-intimal mononuclear infiltration in the systemic veins and pulmonary arteries; ecchymoses of the skin, subcutaneous tissues and mucosa of the gastrointestinal tract, renal pelvis, ureters and epicardium; cirrhosis of the liver, slight.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Intestinal Lipodystrophy (Whipple's Disease)*

PAUL J. SCHUTZ, M.D., WILLIAM H. BENNER, M.D. and WILLIAM A. CHRISTIAN, M.D.

Chicago, Illinois

SINCE 1907 when Whipple first described the entity of intestinal lipodystrophy, twenty-three additional cases presenting similar findings have been reported in the literature. Not all of these can be accepted, either because incomplete histopathologic data have been furnished or because the anatomic findings are somewhat at variance with those Whipple described. Included in the doubtful group are the three early cases described by Pemberton et al.¹⁸ These patients still survive and will probably be reclassified at a later date as acceptable after further observations of their clinical course have been completed. Unfortunately, the diagnosis cannot be made with certainty by clinical study of the living patient because of the non-specific manifestations of the disease. Only one of Pemberton's patients showed gross involvement of the small bowel and in none of the three was a biopsy of the intestine obtained.

As far as can be determined the case we are reporting is the fifteenth that adequately satisfies the criteria described by Whipple. The diagnosis was made post-mortem and was not previously suspected. Our case is noteworthy in the following respects: (1) It closely resembles Whipple's prototype; (2) the patient had been under extended clinical observation at intervals throughout the course of his disease; (3) the laboratory work-up was extensive because of the repeated hospitalizations and uncertainty as to diagnosis.

The syndrome of intestinal lipodystrophy as described by Whipple is "characterized by gradual loss of weight and strength,

stools consisting chiefly of neutral fat and fatty acids, indefinite abdominal signs and a peculiar multiple arthritis." All of the acceptable patients to date, except one,¹⁷ have been males in the fourth, fifth or sixth decades of life. The natural history of the disease is usually protracted, with periods of partial remission followed by recrudescence of the relentless downhill course. Terminally the clinical picture is that of extreme malnutrition and cachexia. Another phenomenon sometimes seen is a generalized increase in skin pigmentation^{1,3,5,14} which may cause confusion with Addison's disease.¹⁶ The migratory arthralgia^{1,3,5,12,13} likewise tends to obscure the true nature of the disease.

Other associated signs and symptoms are anemia, low blood pressure and peripheral pitting edema. These appear late in the disease and are probably secondary manifestations of the poor nutritional status. One patient¹¹ had hemolytic anemia.

Anatomically the only consistent findings have been "massive accumulations of intracellular and extracellular fat in the small intestine and its draining lymph nodes, with dilatation (probably resultant) of lacteals and mesenteric lymphatics."¹⁷ Three patients^{4,5,17} have had chylous ascites but in none has obstruction of the thoracic duct been demonstrated. Fibrous pericarditis, pleuritis and peritonitis have been reported several times but are in no way specific. (Table 1.)

CASE REPORT

The patient, an American-born white male of Italian parentage, was thirty-five years old

* From the Medical and Pathology Services of the Veterans Administration Hospital, Hines, Ill. Published with permission of the medical director, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

when first admitted on May 24, 1946. He stated that he had been in good health until January, 1944. At that time both ankles became swollen and painful following a long road march (he was in service at the time). He soaked his legs in warm water and by the next morning his

X-rays of all joints in both lower extremities failed to reveal arthritic changes. The chest plate was also normal.

At no time during this admission were any manifestations of active arthritis observed. The shoulder disability disappeared and thereafter

TABLE I
PREVIOUSLY REPORTED CASES

Acceptable Cases			Doubtful Cases		
Author	No. of Cases	Year	Author	No. of Cases	Year
Whipple ¹ .	1	1907	Blumgart ² . .	3	1923
Jarcho ³ . . .	1	1936	Fleischmann ⁶	1	1930
Hill ⁹ . . .	1	1937	Collins and Berdez ¹⁵	1	1934
Korsch ⁸ . .	1	1938	Boeck ⁷ . .	1	1937
Glynn and Rosenheim ¹⁶	1	1938	Pearse ¹⁰	1	1942
Reinhart and Wilson ⁴ . . .	1	1939	Pemberton <i>et al</i> ¹⁸	3	1947
Sailer and McGann ⁵	1	1942	Total	10	
Apperly and Copley ¹²	1	1943			
Vaux ¹¹	1	1943			
Amsterdam and Grayzel ¹⁴	1	1945			
Fitzgerald and Kinney ¹¹	1	1945			
Rosen and Rosen ¹⁷	1	1947			
Newman and Pope ¹⁹ .	1	1948			
Chapnick ²⁵	1	1948			
Total	14				

symptoms had subsided. The pain and swelling recurred a few days later after another march. He was hospitalized and given a medical discharge because of an old quiescent osteomyelitis of the right fibula, not because of the arthralgia. In March, 1944, he developed "stiffness" of the knees. Since that time he has had similar involvement of his hands, wrists, elbows, shoulders, back and hips at various times. A sojourn in the southwest and repeated trials of physiotherapy were of no benefit. The past history and family history were non-contributory.

Physical examination revealed a well developed, well nourished white male who was not acutely ill. Oral temperature was 98.6°F., respirations 20, pulse 68, blood pressure 114/80, height 67 inches, weight 155 pounds. He walked slowly and carefully, with short steps, but there was no limp. Physical examination was entirely negative except for slight limitation of abduction and elevation in both shoulders, more marked on the left. None of the joints showed signs of inflammation. Laboratory data are summarized in Table II.

he was asymptomatic. He was discharged on August 21, 1946.

The significance of the joint pains and their relation to this syndrome is unknown. At this time the patient's nutritional state was good and his bowel function was normal. The laboratory data obtained form a valuable base line with which to compare the observations made after the more classic features of the disease had appeared.

The patient re-entered the hospital on August 11, 1947, complaining of weakness, weight loss, abdominal pain aggravated by deep breathing, decreased sexual potency and increased pigmentation of the skin of three months' duration. He stated that the joint pains and swellings had continued from the time of his last admission until about three months prior to this hospitalization. At that time they disappeared and he first became aware of a peri-umbilical pain which was aggravated by deep breathing. He also developed mild dyspnea on exertion and noticed increasing weakness and fatigability. The least activity now exhausted him. He had

lost about 15 pounds in weight, a circumstance he attributed to his lack of appetite. There had been progressive darkening of the skin of the entire body during this same period.

On physical examination oral temperature was 98.6°F., pulse 78, respirations 18 and blood

supplemented with 5 mg. of desoxycorticosterone daily. He showed no improvement and this therapy was discontinued.

A low fat, high carbohydrate, high protein diet and fifteen drops of tincture of belladonna four times a day were prescribed. On this

TABLE II
COLLECTED LABORATORY DATA, FIRST ADMISSION

	May, 1946		June, 1946					
	25	28	13	18	19	22	24	25
Hemoglobin, Gm. 100 cc. of blood	14.0							
R.B.C., millions, cu. mm. of blood	5.1							
W.B.C., thousands, cu. mm. of blood	9.1							
Sedimentation rate, mm. per hr.		12	19	7				
Blood culture					Sterile	Sterile		
Routine urine analysis	Negative							
Wassermann test	Negative							
Bacterial agglutinations				Negative				
N.P.N., mg., 100 cc. of blood	34.2							
Urea N, mg., 100 cc. of blood	14.0							
Uric acid, mg., 100 cc. of blood	4.1							
Cephalin flocculation test				Negative				
A/G ratio, Gm. per 100 cc./Gm. per 100 cc.				3.8/3.7				
Basal metabolic rate						+1	-4	+1

pressure 105/70. He now weighed 140 pounds. There was a gray-brown pigmentation of the skin, most marked on the hands, face and neck. A few, small, shotty nodes were palpable in the groins. He seemed slightly dehydrated. Laboratory data are summarized in Table III.

The electrocardiogram showed right axis deviation, flattening of T_1 , inversion of T_2 and T_3 and slight elevation of $S-T_2$ and $S-T_3$. The T wave was flat in CF_2 and inverted in CF_4 . X-rays of the digestive tract revealed no organic or functional disturbance. A chest plate was also negative.

During the first part of his hospital stay he complained bitterly of abdominal pain and distention not relieved by defecation, and of weakness. There was no diarrhea. Irregularly he ran a low grade fever varying from 99.0° to 99.6°F. With symptomatic treatment directed toward improving his nutritional status, his appetite and sense of well being varied from poor to fair. His weight remained fairly constant at about 140 pounds. Despite the absence of positive laboratory findings he was treated for three weeks for Addison's disease. The treatment consisted of a high sodium, low potassium diet,

management the abdominal symptoms gradually subsided. Early in October he became restless and expressed a wish to return home. He was instructed to continue the dietary and antispasmodic therapy at home and was discharged on October 15, 1947. Despite the symptomatic relief achieved his general physical condition was little better than at the time of admission.

Three years and five months after the onset of the joint pains the patient began to develop signs and symptoms indicative of a systemic wasting disease. Despite clinical evidence of malnutrition the related biochemical findings showed no deficiencies at this time.

No evidence of diminished adrenal or pituitary function could be demonstrated by the laboratory studies. (Table III.) The significance of the elevated basal metabolic rate is obscure. It is without parallel in the literature of Whipple's disease but occurs in about 50 per cent of those with idiopathic steatorrhea.^{26,27} There was no evidence of thyrotoxicosis. The thyroid gland was small and symmetrical, there was no tachycardia, tremor or eye signs, the oral glucose tolerance test was normal, there were no

complaints of insomnia, increased nervousness or heat intolerance, and his appetite certainly was not excessive.

The possibility of hemochromatosis was considered but again no substantiating evidence

On January 27, 1948, he was admitted for the third time. Following his previous hospitalization he had remained weak and underweight although his family doctor had tried various medications in an effort to build up his health

TABLE III
COLLECTED LABORATORY DATA. SECOND ADMISSION

	August, 1947					September, 1947		
	12	13	18	26	30	5	10	18
Hemoglobin, Gm., 100 cc. of blood	14 0		12 0	14 0				12 5
R.B.C., millions, cu. mm. of blood	5 0		4 35	4 6				4 34
W.B.C., thousands, cu. mm. of blood	12 4		12 6	12 8				14 9
Sedimentation rate, mm. per hr		16		23				13 0
Routine urine analysis	Negative		Negative					
Urine culture	Negative							Negative
Urinary urobilinogen, mg. per 100 cc.								0 8
Water test (Kepler)			Normal	Normal			Normal	
Urinary chloride, mg. per 100 cc (Wilder)					54 6			
Bleeding time, minutes						1 5		
Coagulation time, minutes						3 0		
N.P.N., mg., 100 cc. of blood	31 6	34 7						
Urea N, mg., 100 cc. of blood		13 7						
Glucose, mg., 100 cc. of blood		82 3						79 7
CO ₂ combining power, vol., 100 cc. of plasma		44 0	52 0					
Sodium chloride, mg., 100 cc. of blood	618 0	573 0		635 0			638 0	
Potassium, mg., 100 cc of serum	17 0	19 2				21 6		
Sodium, mg., 100 cc of serum		307 2				328 0		
A/G ratio, Gm per 100 cc /Gm. per 100 cc	4 2/2 8							
Cephalin flocculation test								Negative
Thymol turbidity, units								2 0
Bilirubin, mg., 100 cc. of serum								0 5
								No
Bromsulfalcin test								Retention
Amylase, units, 100 cc. of serum								46 1
Cholesterol, mg., 100 cc of plasma								139 0
Cholesterol esters mg., 100 cc of plasma								93 0
Basal metabolic rate		+ 15	+21	+46				
Urinary 17-ketosteroids, mg per 24 hr.								16 2
Urinary prolan A (Cutler and Owen).								Normal
Bacterial agglutinations	Negative							
Kahn and Wassermann tests			Normal		Negative			
Oral glucose tolerance test								

could be found. Hepatic and pancreatic islet function were apparently intact. The exocrine function of the pancreas was not investigated during this admission. Further study was precluded by his insistence on being discharged.

In November, 1947, he had been given a transfusion of 500 cc. of whole blood daily for seven days. This had produced a marked improvement in his strength and well being which persisted until two weeks prior to this admission.

when he again became weak and dyspneic. He also began to develop a rather marked, painless diarrhea, which was worse at night and which was accompanied by abdominal distention. His return at this time was prompted by a desire for more blood transfusions which he believed were very beneficial.

The patient now appeared chronically ill and was quite emaciated. Oral temperature was 98.6°F., pulse 116, respirations 18, blood pressure 104/68 and weight 120 pounds. There were a few crepitant rales audible at the base of the right lung. The abdomen was slightly protuberant and there was moderate generalized tenderness on deep palpation. The liver and spleen were not palpable. The remainder of the examination was not remarkable. Laboratory data are summarized in Table iv. The chest plate showed normal lung fields and a normal cardiac shadow.

Because of a fair blood count he was not given a transfusion. He was placed on a high carbohydrate, high protein, low fat diet fortified with a multivitamin preparation. From January 27th to February 3rd his temperature rose daily to 100°F. After that date it fell to 98.6°F., with an occasional afternoon rise to 99°F. Because of the asthenia suggestive of Addison's disease the Kepler test²² was repeated. Again it was normal.

The diarrhea was not severe, consisting of two or three loose stools daily which were usually passed at night. Following administration of paregoric the consistency of the stools increased and their frequency diminished. A brief course of pancreatin therapy failed to affect the diarrhea appreciably.

He again tired of hospital routine and his failure to improve and insisted on going home. He was discharged on February 17, 1948.

By this time all classic features of the disease were or had been present: loss of weight, weakness, abdominal pain and distention, diarrhea, arthralgia and increased pigmentation of the skin. Again no evidence supporting the diagnoses of Addison's disease, hemochromatosis or hyperthyroidism was elicited by the examiners at the time of admission or by the authors after reviewing the records. The outstanding feature at this time was the continued downhill course, with progressive loss of weight and strength.

The patient was admitted on June 19, 1948, and was observed by one of us (P. J. S.) His complaints at this time were progressive weakness and weight loss and failure of his appetite

to improve. The diarrhea had recurred almost at once following his discharge in February. He averaged about twelve stools daily, with no associated abdominal distress. For four weeks prior to admission the diarrhea had been continuous. The stools were watery, frothy and very

TABLE IV
COLLECTED LABORATORY DATA, THIRD ADMISSION

	January, 1948	February, 1948	
	28	2	12
Hemoglobin, Gm., 100 cc. of blood.....	11.0		
R.B.C., millions, cu. mm. of blood.....	4.56		
W.B.C. thousands, cu. mm. of blood.....	11.6		
Hematocrit.....	35.0		
Routine urine analysis.....	Negative		
Kahn test.....	Negative		
N.P.N. mg., 100 cc. of blood	34.2		
Glucose, mg., 100 cc. of blood.....	80.0		
Cholesterol, mg., 100 cc. of plasma.....	119.0	
Cholesterol esters, mg., 100 cc. of plasma.....	76.0	
Serum bilirubin, mg., 100cc. of serum.....	0.5	
Phosphorus, mg., 100 cc. of serum.....	4.0	
Alkaline phosphatase (Bodansky units).....	4.6	
Amylase, units, 100 cc. of serum.....	34.0	
Lipase, cc. of N/20 NaOH per cc. of serum.....	1.1	
Thymol turbidity.....	2.0	
Potassium, mg., 100 cc. of serum.....	20.4	
Urea N, mg., 100 cc. of plasma.....	12.0
Sodium chloride, mg., 100 cc. of plasma.....	632.0
Water test.....	Normal

foul-smelling. He frequently noticed undigested food, such as green beans and corn, in the stool. The color of the stool varied from gray to yellow-brown. Since February he had lost 16 pounds in weight and during this time had noticed progressive swelling of his ankles and legs. This edema showed no diurnal variation.

On physical examination the patient was markedly cachectic. Oral temperature was 98.6°F., pulse 100, respirations 20, blood pres-

TABLE V
COLLECTED LABORATORY DATA. LAST ADMISSION

	June, 1948						July, 1948	
	20	22	23	25	29	30	7	8
Hemoglobin, Gm., 100 cc. of blood.....	12 0		12.0					
R.B.C., millions, cu. mm. of blood	3 83		4 22					
W.B.C., thousands, cu. mm. of blood.....	7 8		9 1					
Platelets, thousands, cu. mm. of blood.....	229.8							
Clotting time, minutes..	5 0							
Bleeding time, minutes..	2 0							
Prothrombin time, seconds	14							
Mean corpuscular volume, cu. micra.....		87						
Mean corpuscular hemoglobin, micromicrograms.....		26						
Color index.....		0 83						
Hematocrit.....			34					
Routine urine analysis..	Negative							
Glucose, mg., 100 cc. of blood (fasting).....						50		
N.P.N., mg., 100 cc. of blood						46 8		
Potassium, mg., 100 cc. of serum							15 4	
A/G ratio, Gm. per 100 cc./Gm. per 100 cc.		1 8/1 7				2 4/1 8		
Cephalin flocculation test			Negative					
Thymol turbidity test.			0			1 0	1 0	
Butter-choline fat absorption test (Popper et al.) ..					Abnormal, very deficient			
Bilirubin, mg., 100 cc. of serum	0 15							
Cholesterol, mg., 100 cc. of plasma....	86					72		
Cholesterol esters, mg., 100 cc. of plasma....	59							
Kahn and Wassermann tests	Negative							
Oral glucose tolerance ..						Abnormal low curve		
Calcium, mg., 100 cc. of serum			7 5					
Phosphorus, mg., 100 cc. of serum			2 8				2 3	
Alkaline phosphatase (Bodansky units).....							3 8	
Vitamin A, micrograms, 100 cc. of blood ..		20 0						
Carotene, micrograms, 100 cc. of blood.....		0						
Weight of "wet" stool, Gm. per 24 hr..		781 0				145 0		211 0
Total stool nitrogen, Gm. per 24 hr.....						0 99		
Total stool fat, Gm. per 24 hr		20 87						3 47
Stool fatty acids, Gm. per 24 hr		13 81						2 22
Stool neutral fat, Gm. per 24 hr		7 8						1 25
Stool culture.....			Negative				Negative	
Gastric acidity (free and total)				Normal				

sure 96/64 and weight 102 pounds. The skin showed a dusky, gray-brown pigmentation. The sclerae were not icteric. There was slight atrophy of the mucosa of the free margin of the tongue but no frank glossitis or stomatitis. A small amount of mucopurulent material was adherent to the posterior pharyngeal wall. The chest and abdomen showed extensive wasting of the superficial tissues and musculature. The breath sounds were accentuated and bronchovesicular in character over both lungs. The heart was normal. The abdomen was slightly distended, somewhat tense and there was slight generalized tenderness. The liver, spleen and kidneys were not palpable. The fingers showed early clubbing. The laboratory data are summarized in Table v.

X-rays of the chest were negative. Gastrointestinal films showed hypermotility of the stomach and a small bowel pattern considered characteristic of chronic nutritional deficiency. There was segmentation of the intestinal loops, coarsening of the mucosal pattern and a tendency of the barium to puddle. (Fig. 1.) The gallbladder readily concentrated the radiopaque dye.

At the time of admission the patient was passing about twelve mushy, gray-tan stools daily. They were frothy, foul-smelling, bulky and contained gross particles of undigested food. He was placed on a high carbohydrate (low in polysaccharide content), high protein, low fat diet. Other therapy given included brewers' yeast, multivitamins, parenteral vitamin B complex, vitamin K, crude and refined liver extract, folic acid, pancreatin, and daily blood and plasma transfusions. The number of stools diminished somewhat, as did the total bulk of feces, but the character of the excreta remained unchanged. Because of the low serum vitamin A level 75,000 units of vitamin A were given daily.

His nutritional state continued to deteriorate despite all therapeutic efforts. His daily food intake varied from 300 to 1,900 calories. Intravenous alimentation was difficult because of his tendency to develop pulmonary edema after receiving small quantities of fluids. The pitting edema of the legs resisted all efforts at treatment, including mercurial diuretics.

On July 8th he passed a large amount of dark, red blood via the rectum. He was given 1,000 cc. of whole blood. Two days later he expired suddenly, having remained conscious until an hour before his death.

During the last admission the patient was



FIG. 1. X-ray of small bowel showing an early stage of disordered motor function due to nutritional deficiency. Note coarsening of mucosal pattern and dilatation of intestinal loops. An early moulage sign is seen.

studied from two standpoints, one diagnostic, and the other nutritional. Although the stools appeared to contain an excessive amount of fat clinically, this was not conclusively established. Fecal fat content, both normal and pathologic, is measured in percentage of the dried twenty-four-hour fecal output.²⁰ In this case the stools were weighed in the fresh "wet" state, and the fat fractions were extracted without previously dehydrating the specimen. Thus Fowweather's first criterion could not be applied to these data, and it cannot be definitely stated that a relative increase in total fat content of the feces existed. However, the quantities of neutral fat and fatty acid were accurately assayed and on two occasions these values were within normal limits. (Table v.)

Despite the difficulty in evaluating laboratory data the patient was clinically considered to have steatorrhea. Four conditions were considered in the differential diagnosis: biliary tract disease, pancreatic insufficiency, idiopathic steatorrhea and tuberculous mesenteric adenitis.

Normal visualization of the gallbladder, absence of jaundice and presence of urobilinogen in the urine established the normalcy of the biliary tract. Pancreatic steatorrhea was ruled out by the preponderance of hydrolyzed fat in the stool, absence of azotorrhea and lack of response to oral pancreatic extract.

Idiopathic steatorrhea was next considered.

In addition to the wasting, asthenia, diarrhea and skin pigmentation, the following points of similarity were found when our data were compared with the criteria tabulated by Bockus:²⁷ (1) homogeneous greasy stool; (2) about 35 per cent of fecal fat excreted as neutral fat and 65 per cent as fatty acids and soap; (3) excretion of nitrogen in the stool less than 3.5 Gm. for a twenty-four-hour period; (4) fasting hypoglycemia; (5) a flat, oral glucose tolerance curve; (6) evidence of low blood lipids and low fat tolerance; (7) low blood cholesterol; (8) low serum calcium; (9) elevated basal metabolic rate (on previous admission, not checked before death); (10) anemia and (11) low plasma proteins.

There were, however, some important links missing from the chain of evidence. The most obvious deficiency was the absence of macrocytic hyperchromic anemia. It is known that the anemia associated with idiopathic steatorrhea may vary from simple hypochromic anemia in the early stages and during periods of remission to one indistinguishable from pernicious anemia in the later advanced stages of the disease.²⁶ Furthermore, it has been shown that when the anemia is in a macrocytic hyperchromic phase parenteral administration of liver extract may be followed by a fall in the color index to a value less than unity. The anemia then responds to iron therapy exactly like any secondary anemia due to iron deficiency.²⁵ Since our patient was in an advanced stage of the illness, the absence of hyperchromia and macrocytosis was difficult to explain.

The essential normality of the mucous membranes of the mouth and tongue was the second discordant factor. One of the most characteristic features of the sprue syndrome is the appearance of crops of vesicles on the tongue and lining of the cheek, which later rupture and form painful aphthous ulcers. With the exception of minimal atrophy of the papillae along the margin of the tongue, there was no evidence of recent or old stomatitis or glossitis in our patient.

Because of these discrepancies in the clinical picture a clear cut diagnosis of idiopathic steatorrhea could not be made. The possibility of tuberculous mesenteric adenitis was not considered seriously because the patient was not toxic, the lungs were free of disease and the bulk of evidence was in favor of some defect of intestinal absorption.

As a secondary problem the pathophysiologic

basis of the patient's poor nutritional state was investigated. Attention was focused on the capacity of the bowel to digest and absorb fat. Recently it has been shown by Popper *et al.*²⁴ that when a standard amount of fat and lipotropic substance (e.g., butter and choline) are ingested the subsequent rise of serum thymol turbidity is an accurate index of the intestinal ability to absorb fat. The normal individual will show a rise in thymol turbidity of 200 to 400 per cent over the fasting level. Using this test we found that the thymol turbidity test, both before and after ingestion of the butter-choline mixture, was consistently negative (i.e., there was no detectable turbidity in the solution). This was interpreted as indicating that little if any fat was being absorbed from the bowel. When rechecked the next day the thymol turbidity was 1.0 units, tending to corroborate the low values previously obtained. The deficiency of intestinal fat absorption was also manifested by the low serum calcium and by the low serum vitamin A level which on one occasion was 19.5 micromicrograms (10.9 micromicrograms as ester, 8.6 micromicrograms as the alcohol).

A similar defect in carbohydrate absorption was evidenced by the low flat curve obtained with the oral glucose tolerance test.

It was concluded that the patient was suffering from an obscure metabolic defect, characterized by decreased absorptive efficiency of the intestinal tract, closely resembling idiopathic steatorrhea. Further studies were interrupted by the patient's death.

AUTOPSY FINDINGS

At autopsy the essential findings were confined to the abdomen. There were 1,500 cc. of straw-colored fluid in the peritoneal cavity. The small intestine was rather opaque and homogeneous grayish yellow in color. There was no suggestion of a lacteal pattern grossly, but the intestinal wall was grossly infiltrated to about three times normal thickness. This thickening was diffuse and uniform and involved all of the small bowel. On opening the bowel there was a moderate amount of dark bloody fluid along its entire course. The mucosal folds were somewhat thickened and prominent but showed symmetrical arrangement. There were scattered petechial hemorrhages in the mucosa, more profuse in the distal two-thirds of the ileum, where they became confluent and gave a diffuse

hemorrhagic appearance to large areas. There were no gross ulcerations anywhere in the gastrointestinal tract. The hemorrhagic character of the intestinal mucosa ended abruptly at the ileocecal valve. The esophagus, stomach and colon were entirely normal.

The most conspicuous abnormality was found in the mesentery of the small bowel. (Fig. 2.) There were numerous pinkish-gray lymph nodes measuring up to 3 cm. in their greatest diameter. They were sometimes separate, more often adherent to several others. These masses of nodes, although apparently confluent, showed no actual fusion as the individual nodes were well demarcated on cut section. The general contour of the nodes was symmetrical, their enlargement being concentric. The cut surface of all the nodes showed a finely honeycombed, spongy appearance. The spaces contained an amber, clear, liquid greasy material which could easily be expressed.

The thickening of the mesentery was found to be due to the extensive adenopathy and not to any intrinsic infiltration. Similar lymph node enlargement was also found at the origin of the coeliac axis artery and among the pre-aortic nodes. The peribronchial, mediastinal and superficial lymph nodes were not involved. The other abdominal and thoracic viscera and the endocrine glands were grossly normal.

Microscopic sections taken from the duodenum, jejunum and ileum showed uniform involvement which was characterized by a heavy infiltration of the mucosa with foam cells. These mononuclear macrophages were arranged in dense sheets, filling in particular the villi, which were thick, club-like and top heavy. (Fig. 3.)

The stroma of the mucosa contained numerous, large, empty vacuoles measuring from fifty to several hundred micra in diameter. The cellular infiltration and the vacuolization had greatly distorted the normal mucosal pattern. The submucosa was also thickened and contained many ovoid and elongated channels, some of which were lined by endothelial cells while the walls of others apparently consisted only of a condensation of the connective tissue stroma. Frozen sections stained with Sudan iv revealed that the small droplets in the cytoplasm of the foam cells readily took the fat stain. The large vacuoles in the submucosa everywhere contained a homogeneous material which also stained brilliantly with Sudan iv. (Fig. 4.)

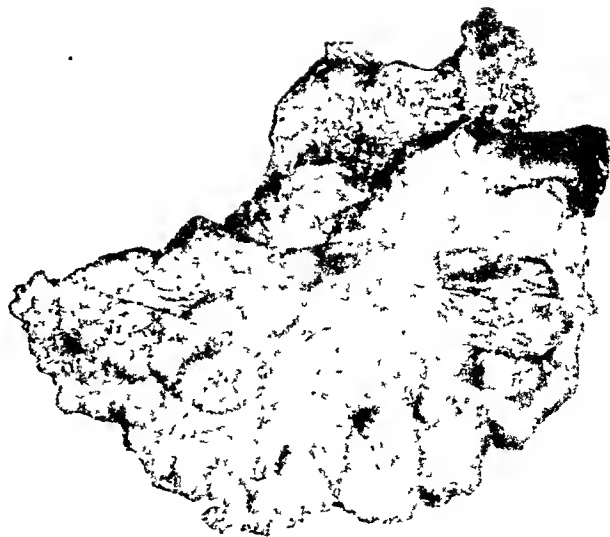


FIG. 2. Mesentery of small bowel demonstrating extensive lymphadenopathy.

The muscular coat of the bowel showed no hypertrophy. The serosa was slightly swollen and contained scattered round cells. Occasionally, dilated lymph channels were seen in the subserosa but they were much less prominent than in the submucosa. Neither inflammatory exudate nor giant cells could be found in the various layers of the bowel wall.

The mesenteric nodes universally presented similar changes. The honeycomb effect produced by the vacuoles was even more prominent microscopically than grossly. Everywhere throughout the nodes were ovoid spaces of varied size. They appeared to be lined with a single layer of endothelial cells. The parenchyma of the nodes was greatly reduced in amount, being compressed into irregular strands and trabeculae between the dilated spaces. The architecture was completely obscured. Rarely, a lymph follicle could be delineated. The irregular columns of parenchymal tissue consisted of a haphazard mixture of reticulo-endothelial cells, scattered lymphocytes, islands of foam cells similar to those in the intestinal mucosa, a few neutrophils and a scanty connective tissue framework. Occasional giant cells were found, sometimes lying in the lumina of the vacuoles but usually in the subjacent stroma forming the wall of the space. (Fig. 5A.) These cells contained from three to ten nuclei which were uniform in size and scattered throughout the cytoplasm. The honeycombing of the parenchyma with lipid-containing vacuoles was uni-

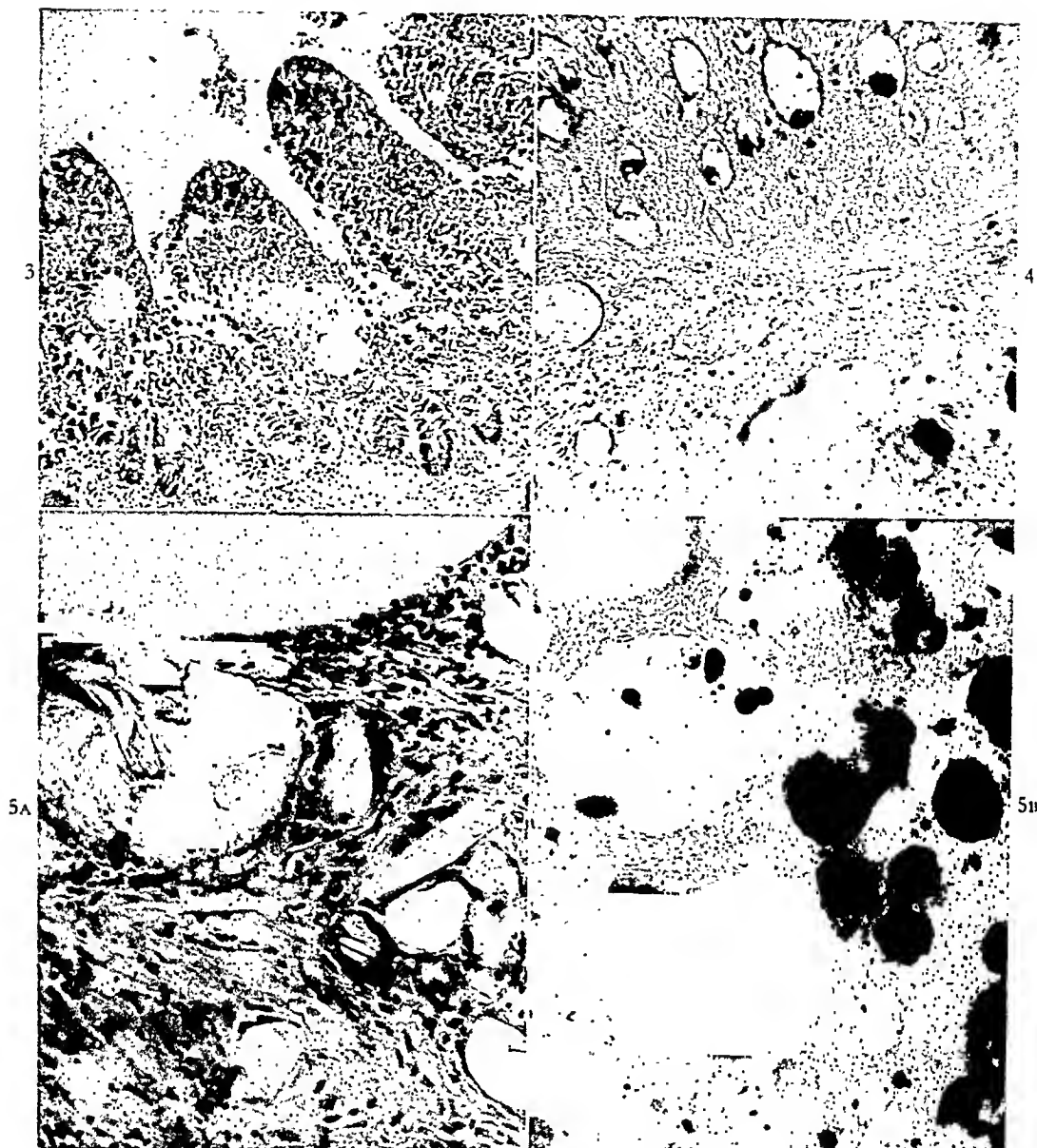


FIG. 3. Intestinal mucosa showing thickening of the villi and compression of stroma by mononuclear foam cells and large vacuoles.

FIG. 4. Small bowel; the distended lymphatics and vacuole-like spaces contain material staining deep orange with Sudan IV.

FIG. 5. A, lymph node; foreign body giant-cell reaction at the margin of a large vacuole. B, the many vacuoles in the nodes, as in the intestinal mucosa, contain material staining an intense orange with Sudan IV.

form in all nodes but the relative frequency of the giant cells varied from node to node.

Frozen sections stained with Sudan IV showed that all the spaces contained a homogeneous substance which stained an intense orange. (Fig. 5B.) The connective tissue capsule of the various nodes showed marked fibrous thickening and contained many dilated lymph channels.

The rest of the gastrointestinal tract, liver,

spleen, pancreas, kidneys, adrenals, thyroid, prostate and lungs were microscopically normal. The myocardium showed areas of brown atrophy characterized by collections of golden brown pigment granules at the poles of the nuclei. The staining quality of these granules with Sudan IV was poor and inconsistent.

The pathologic diagnoses were malnutrition, ascites (non-chylous), brown atrophy of the heart and intestinal lipodystrophy.

CONCLUSIONS

A case of intestinal lipodystrophy is presented. The syndrome should be considered in the differential diagnosis of protracted diarrhea, especially when the patient is a male in middle life. The diagnosis can only be presumptive before death unless adequate surgical biopsies are done at laparotomy.

This case sheds no light on the etiology of intestinal lipodystrophy but demonstrates the importance of poor intestinal absorption in producing the final cachectic phase. Intestinal lipodystrophy may closely simulate clinically most of the features of idiopathic steatorrhea.

Acknowledgments. We wish to express our gratitude to Dr. Smith Freeman of Northwestern University and Drs. Frederick Steigmann and Hans Popper of Cook County Hospital and Hektoen Institute for their courtesy in making their laboratory facilities available to us.

REFERENCES

- WHIPPLE, G. H. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. *Bull. Johns Hopkins Hosp.*, 18: 382-391, 1907.
- BLUMGART, H. L. Three fatal adult cases of malabsorption of fat. *Arch. Int. Med.*, 32: 113-128, 1923.
- JARCHO, S. Steatorrhea with unusual intestinal lesions. *Bull. Johns Hopkins Hosp.*, 59: 275-286, 1936.
- REINHART, H. L. and WILSON, S. J. Malabsorption of fat (intestinal lipodystrophy of Whipple). Report of a case. *Am. J. Path.*, 15: 483-491, 1939.
- SAILER, S. and MCGANN, R. S. Lipophagic granulomatosis, of the enteric tract. *Am. J. Digest. Dis.*, 9: 55-63, 1942.
- FLEISCHMANN, R. Über tumorbildende Fettgewebsgranulom in Nekrose des Dunndarms. *Arch. f. klin. Chir.*, 158: 692-701, 1930.
- BARGEN, J. A., BOLLMAN, J. L. and KEPLER, E. J. The diarrhea of pancreatic insufficiency. *Am. J. Digest. Dis.*, 4: 728-732, 1938.
- KORSCH, H. J. Fettstoffwechselstörung mit Granulombildung im Mesenterium. *Zentralbl. f. allg. Path. u. path. Anat.*, 71: 337-344, 1938-1939.
- HILL, J. M. Mesenteric chyladenectasis. Report of a case. *Am. J. Path.*, 13: 267-275, 1937.
- PEARSE, H. E. Whipple's disease, or intestinal lipodystrophy. *Surgery*, 11: 906-911, 1942.
- FITZGERALD, P. J. and KINNEY, T. D. Intestinal lipodystrophy. *Am. J. Path.*, 21: 1069-1089, 1945.
- APPERLEY, F. L. and COPLEY, E. L. Whipple's disease (lipophagia granulomatosis). *Gastroenterology*, 1: 461-470, 1943.
- VAUX, D. M. Chyladenectasis with steatorrhea. *J. Path. & Bact.*, 55: 93-96, 1943.
- AMSTERDAM, H. J. and GRAYZEL, D. M. Intestinal lipodystrophy (lipophagia granulomatosis or Whipple's disease). *Am. J. M. Sc.*, 210: 605-611, 1945.
- COLLINS, A. N. and BERDEZ, G. L. Chyle cysts of the mesentery. *Arch. Surg.*, 28: 335-344, 1934.
- GLYNN, L. E. and ROSENHEIM, M. L. Mesenteric chyladenectasis with steatorrhea and features of Addison's disease. *J. Path. & Bact.*, 47: 285-290, 1938.
- ROSEN, M. S. and ROSEN, S. H. Intestinal lipodystrophy of Whipple. *Am. J. Path.*, 23: 443-466, 1947.
- PEMBERTON, J. DEJ., COMFORT, M. W., FAIR, E. and ZASLOW, J. Intestinal lipodystrophy (Whipple's disease); a preliminary report of three cases in an early stage of the disease. *Surg., Gynec. & Obst.*, 85: 85-91, 1947.
- NEWMAN, B. and POPE, R. H. A case of intestinal lipodystrophy (Whipple's disease) simulating Boeck's sarcoid. *Gastroenterology*, 11: 120-126, 1948.
- FOWWEATHER, F. S. The determination of the amount and the composition of the fat of the faeces. i. Investigation of a "wet" method and comparison with the "dry" method. *Brit. J. Exper. Path.*, 7: 7-14, 1926. ii. The composition of the fat of the faeces of the normal adult, as ascertained by the "wet" method, together with the results in certain pathologic conditions. *Ibid.*, 7: 14-21, 1926.
- CUTLER, H. H., POWER, M. H. and WILDER, R. M. Concentrations of chloride, sodium, and potassium in urine and blood. Their diagnostic significance in adrenal insufficiency. *J. A. M. A.*, 111: 117, 1938.
- KEPLER, E. J., ROBINSON, F. J. and POWER, M. H. Diagnostic value of certain studies in cases of Addison's disease. *J. A. M. A.*, 118: 1404, 1942.
- CUTLER, M. and OWEN, S. E. Clinical value of prolan, a determination in teratoma testis. *Am. J. Cancer*, 24: 318-325, 1935.
- POPPER, H., STEIGMANN, F., DYNIEWICZ, H. and DUBIN, A. Use of thymol turbidity as lipid absorption test. Experiences with thymol turbidity and zinc sulfate turbidity test under physiologic and pathologic conditions. *J. Lab. & Clin. Med.*, in press.
- MACKIE, T. T. Nontropical sprue., *M. Clin. North America*, 17: 165-184, 1933.
- BODANSKY, M. and BODANSKY O. Biochemistry of Disease, pp. 204-219. New York, 1946. The Macmillan Co.
- BOCKUS, H. L. Gastroenterology. Vol. 2, pp. 229-247. Philadelphia, 1944. W. B. Saunders Co.
- CHAPNICK, H. A. Idiopathic steatorrhea, with report of a case of Whipple's disease. *Ann. Int. Med.*, 29: 549-558, 1948.

Thrombocytopenic Purpura Complicating Radioactive Phosphorus Treatment in a Patient with Polycythemia Vera*

GOULD A. ANDREWS, M.D.

Ann Arbor, Michigan

BECAUSE of the rapidly increasing use of radioactive elements in the treatment of disease, possible undesirable effects of these materials are of considerable importance. The present report concerns a patient with polycythemia vera who developed thrombocytopenic purpura associated with striking morphologic changes in the megakaryocytes after treatment with radioactive phosphorus.

It has been clearly established that P^{32} given internally in therapeutic doses is capable of depressing all of the major hemopoietic elements of the marrow with corresponding changes in the peripheral blood. Following a therapeutic dose the white blood cells and platelets may be depressed quite promptly within the first six weeks; the leukopenia is usually maximal somewhat before the thrombocytopenia. Decrease in the red blood cells is more delayed and usually is not noted until the white cells and platelets have begun to return toward normal. The sequence of changes in the blood is presumably related to the normal rate of maturation and length of survival of the different formed elements.

Several reports indicate that in some instances thrombocytopenia may be the most important undesirable effect of radioactive phosphorus therapy. Hall, Watkins, Hargraves and Giffin¹ reported the cases of twelve patients with polycythemia vera treated with P^{32} and noted significant thrombocytopenia in four patients. the

lowest platelet counts ranging from 29,000 to 86,000 per cu. mm. The maximal depression of platelet values occurred in one to two months after the medication was given. There was no clinical purpura except for the occurrence of petechiae on the lower extremities in these patients.

Hempelman, Reinhard, Moore, Bierbaum and Moore² reported a group of one hundred patients with various hematologic disorders who were treated with radioactive phosphorus. Some of the thrombocytopenia noted may have been a part of the original disease rather than a result of treatment, but the authors believed that the P^{32} contributed to a significant fall in platelets in forty-four patients. Among eighteen patients with polycythemia vera there were two in whom the platelet counts fell to below 100,000 per cu. mm., and one in whom the value was below 50,000 per cu. mm. One fifty-nine year old woman with polycythemia vera was given 7.56 mc. of radioactive phosphorus orally and about one month later developed a platelet count as low as 29,000 per cu. mm. At this time the patient had petechiae on the lower extremities but no other purpuric manifestations. There was spontaneous recovery from this episode of thrombocytopenia.

CASE REPORT

The patient, E. R., was a sixty-seven year old, white, married woman who was referred to the Simpson Memorial Institute in May, 1947. She

* From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Mich.

gave a history of loss of strength and decrease in weight which had begun about two years previously. At about the same time she had noticed varicose veins of her lower extremities and these had been treated by injection and ligation. About a year after the onset of these

cell count and hemoglobin remained definitely elevated.

When the patient was examined in May, 1947, she showed evidence of weight loss and there was distinct cyanosis of the skin and mucous membranes. Retinal veins were greatly

TABLE I
HEMATOLOGIC CHANGES FOLLOWING TREATMENT WITH RADIOACTIVE PHOSPHORUS

Date	Red Cells (million)	Hemoglobin (Gm.)	Hematocrit (percent)	Platelets	White Cells	Neutrophils	Lymphocytes	Monocytes	Eosinophiles	Basophiles
May 13, 1947.... Phlebotomy	8.9	17.5	66	115,000	14,900	69	11	19	1	0
May 28, 1947.... P ³² 8.4 mc.	7.1	16.8	62	117,000	13,300	71	17	11	0	1
July 9, 1947.....	6.8	15.5	54	Below 5,000	7,250	70	20	9	1	0
July 23, 1947....	5.1	11.0	42	Below 5,000	4,100	30	47*	20	3	0
August 5, 1947...	4.5	11.0	36	23,000	2,450	34	54	12	0	0
December 2, 1947	5.0	15.9	44	55,000	6,400	60	28	12	0	0
March 5, 1948...	4.4	13.3	41.5	44,000	7,450	62	29	9	0	0

* A few "irritation" lymphocytes were noted on this day.

symptoms she became more seriously ill with dizziness, anorexia and shortness of breath on exertion. At that time it was first noted that her eyes were becoming injected and her lips were a dusky purple. Three or four months later, in November, 1946, it was found that her spleen was enlarged and that the blood picture was that of polycythemia. Several phlebotomies were performed. Early in 1947 the patient suddenly lost consciousness while descending her cellar stairs, fell and suffered a laceration of her forehead. Following this accident there was paralysis of the right lower extremity and a diagnosis of cerebrovascular accident was made. There was quite a prompt recovery from the paralysis and the patient was started on a course of x-ray therapy by her local physician, using 200 kv. irradiation with added filtration of 0.5 mm. Cu and 1.0 mm. Al, 50 cm. target skin distance. Between January 8th and January 27, 1947, she received 30r in air to one field per day, to a total of 60r to each of four fields over the anterior and posterior trunk. Between February 18th and February 26, 1947, she was given 200r to each of six small fields over the spine, sternum and extremities.

The irradiation treatment was followed by some improvement in symptoms and partial correction of the blood values but the red blood

dilated and of a deep red color. The blood pressure was 156/92. The liver border was felt just below the right costal margin and the spleen extended 3 cm. below the left rib margin on inspiration. There were varicose veins of the lower extremities and stasic dermatitis was present. Chest x-ray was normal except for pleural scarring and calcified nodes. The urine contained a 1+ albumin but was otherwise normal.

On the basis of the clinical findings and the blood values the diagnosis of polycythemia vera was confirmed. (Table I and Fig. 1.) Phlebotomy was done on May 13, 1947, and the patient was asked to return on May 28th, at which time she was given approximately 8.4 mc. of radioactive phosphorus intravenously and was allowed to return to her home. About five weeks later the patient's personal physician called and said that the patient "looked as if she had been in an automobile accident" with extensive ecchymoses and purpuric lesions. She was hospitalized on July 9, 1947, at the Simpson Memorial Institute and stated that she had apparently been improving until late in June when she had noted tiny red blotches on her lower extremities followed in a few days by the spontaneous appearance of large bruises. She also noted the onset of almost continuous gradual bleeding

from her nose. Examination showed very extensive petechiae and large ecchymoses, the latter being largely limited to the extremities. There were multiple areas of oozing from the mucous membranes of both sides of the nose. The remainder of the examination was essen-

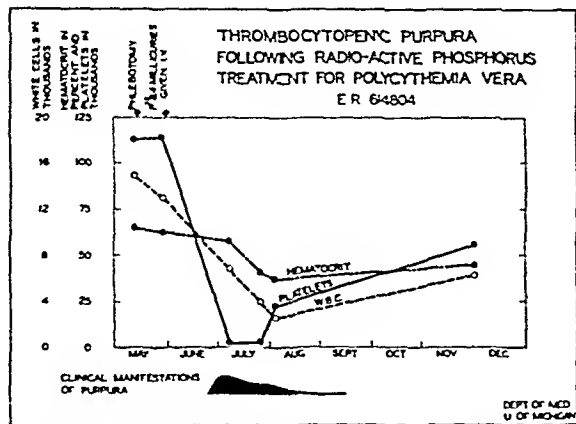


FIG. 1. Graphic representation of hematologic changes.

tially as it had been two months earlier except for some decrease in the general erythema.

Blood studies showed some fall in red cell values and a distinct decrease in the white cell count. Platelets were almost absent. Clotting time (Lee-White) was five minutes; bleeding time (Duke) was ++++ prolonged (more than twenty minutes). There was no clot retraction in three hours. The tourniquet test was strongly positive. Sternal puncture was done. There was a cellular marrow with developing erythrocyte and granulocyte forms present in normal ratio showing essentially normal distribution of various stages of maturity. Developing eosinophiles were fairly prominent. Granulocytic forms showed slight vacuolation but no pronounced basophilic granulation of the cytoplasm. Plasma cells were relatively increased in number and included some large multinucleated forms. Megakaryocytes were present in approximately normal numbers but practically all of them showed striking morphologic changes. They were extremely variable and some could be identified as megakaryocytes only because there were transitional forms between these extremely bizarre structures and megakaryocytes of unequivocal identity. In many the cytoplasm appeared to be fragile, projecting out in long formless wisps. In some it appeared more dense, with multiple vacuoles and in some it was a distinct, well formed meshwork. There were

some condensations in the cytoplasm which may have represented abnormal maturation of large platelet forms. The nuclei of the megakaryocytes lacked lobulation but there were frequently two or more nuclei per cell. The chromatin tended to form a coarse, loose pattern in many of these nuclei. (Figs. 2 to 4.)

The patient was kept at bed rest and given repeated doses of from 100 to 250 cc. of blood plasma intravenously. There appeared to be some temporary improvement in the nasal bleeding with each injection of plasma. It was thought that loss of blood from the nose was sufficient to contribute significantly to the fall in red cell values. No transfusions of whole blood were given. There were repeated crops of petechiae with a general tendency toward a diminution in number. Over a period of three weeks there was gradual decrease in the ecchymoses while the nasal oozing became intermittent and finally stopped. The patient returned home on August 7, 1947. She was seen again three weeks later when she appeared to be getting along well; there were no purpuric manifestations. However, the tourniquet test was still positive in moderate degree.

On December 2, 1947, the patient was again seen for follow-up. She was feeling entirely well, with good general strength. The spleen was not palpable. There were no purpuric manifestations but the tourniquet test showed slight residual increased capillary fragility. Clotting time was seven minutes. Bleeding time five and one-half minutes. Clot retraction was good in one hour. Sternal puncture was repeated and again showed a cellular marrow with normally developing erythrocyte and granulocyte elements. The proportion of developing erythrocytes to granulocytes was approximately 1:2. Megakaryocytes were present in at least normal numbers. Although a minority of these showed the unusual morphology seen in the first marrow study, most were essentially normal. Many of them appeared rather young and had a relatively small amount of cytoplasm. Only rarely was definite evidence of platelet maturation noted in the cytoplasm. (Fig 5)

The most recent out-patient visit was made on March 5, 1948. The patient had been feeling very well but had had a recurrence of petechiae over the upper extremities late in February when she had been very active doing house cleaning. These petechiae had cleared spontaneously. The examination was otherwise the

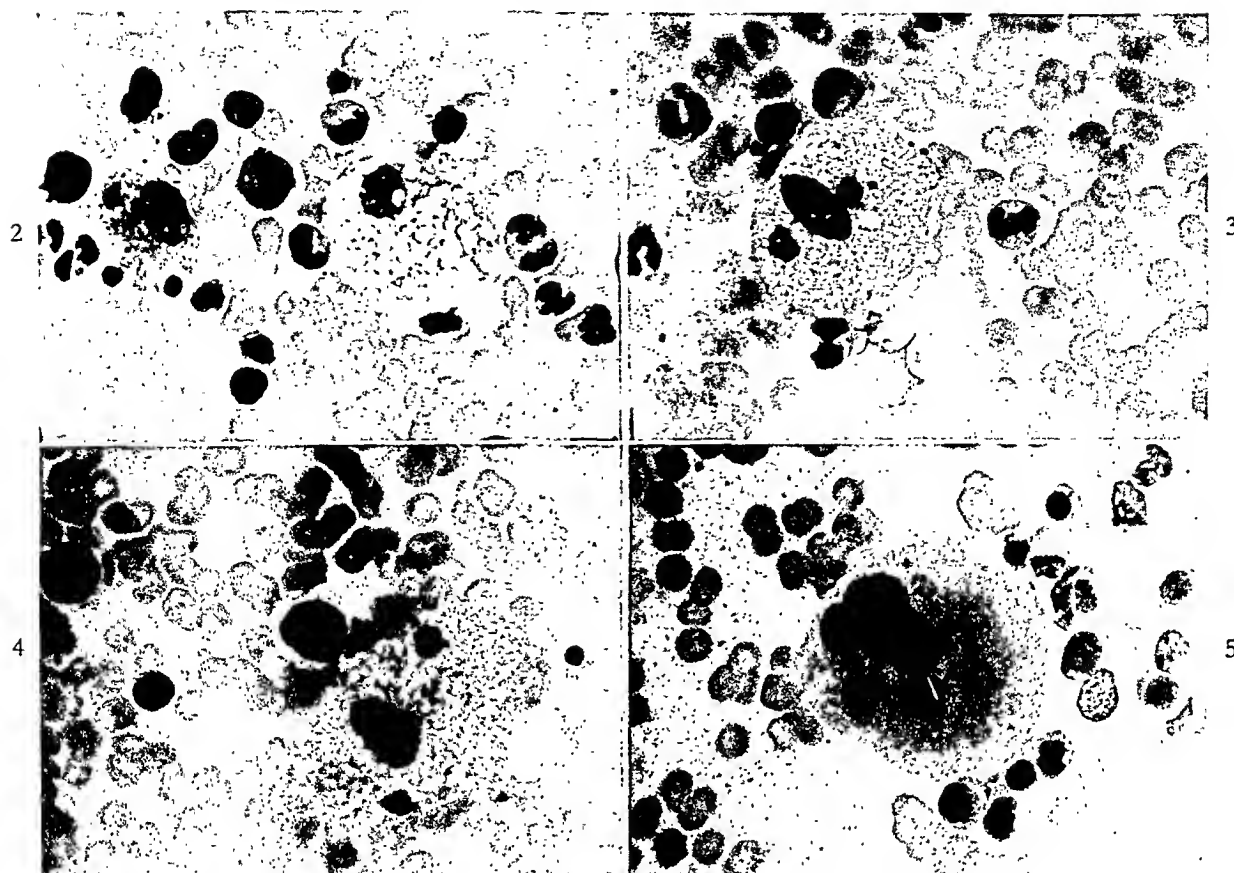


FIG. 2. Photomicrograph of sternal marrow obtained during acute purpuric episode and showing two very abnormal cells believed to be megakaryocytes.

FIGS. 3 and 4. Atypical megakaryocytes from the same sternal puncture.

FIG. 5. From material obtained eight months later, after platelets had increased. This shows a relatively normal megakaryocyte.

same as in December, 1947. The tourniquet test was slightly less positive than it had been at that time.

The blood values shown in Table 1 were determined by standard methods. Platelets were counted on carefully spread blood films prepared on cover slips previously spread with cresyl blue and later stained with Wright's stain. The platelet values were determined by counting the number of platelets seen per 1,000 red cells and calculating the total on the basis of simultaneously done red counts. During the recovery phase many of the platelets were very large.

COMMENTS

This patient had typical polycythemia vera but even before treatment was given the platelets were somewhat below the average normal values and distinctly below the increased levels usually present in polycythemia vera. X-ray therapy which had been given about four months before the P^{32} undoubtedly had some depressing effect upon the bone marrow and may have been,

in part, the cause for the mild thrombocytopenia which was present when the patient was first seen by us. However, there had been enough time for manifestation of the maximal effect of this x-ray therapy before the radioactive phosphorus was given. This dosage of radioactive phosphorus had not been found excessive in other patients with the same disease. It is believed that the profound thrombocytopenia which developed in this patient was an exaggeration of the usual decrease in platelets caused by P^{32} treatment. Probably the severity of the thrombocytopenia was conditioned by a pre-existing tendency toward inadequacy of platelet formation which had not been clinically apparent. There are undoubtedly other factors which influence individual variations in response.

The experience with this patient as well as the course of other patients treated by us suggests that individuals who have low platelet counts before therapy are more

likely to suffer severe thrombocytopenia after P^{32} is given than are those who have normal or high platelet counts at the outset. Thus it would appear that this form of treatment should be used with caution, if at all, in patients with decreased platelets.

Although the number is limited, all reported patients with this complication of radioactive phosphorus treatment have made spontaneous recoveries from thrombocytopenia unless the underlying blood disorder contributed to a fatal outcome. However, there seems little doubt that fatal hemorrhage might result from radioactive phosphorus alone if the dose were really excessive.

The striking morphologic changes noted in the megakaryocytes of the marrow during the purpura were probably a result of the radioactive phosphorus. It is unfortunate that no pretreatment sternal puncture was done. If the megakaryocyte changes had been shown to be absent before treatment, this would lend support to the supposition that they were due to the P^{32} . There is little doubt, however, that the abnormality of the megakaryocytes was associated with the thrombocytopenia and the latter occurred at about the same length of time after treatment as in other reported cases of purpura induced by radioactive phosphorus. If further experience shows that these megakaryocyte changes are characteristic in irradiation-induced thrombocytopenia, they may be of considerable interest and occasionally may be of value in diagnosis. The morphology of these megakaryocytes is entirely different from

that seen in idiopathic thrombocytopenic purpura.

There is no established treatment for this type of irradiation-induced purpura. Our patient was given rest, plasma and symptomatic measures. Blood transfusions would undoubtedly be helpful in combating anemia and might cause temporary improvement in capillary permeability. Artificially induced phosphorus diuresis might increase the excretion of the radioactive material but would probably be of little practical value after the onset of purpura. In view of the bone marrow picture and the lack of evidence indicating that the spleen plays a role in this type of thrombocytopenia it is doubtful that splenectomy would be of value.

SUMMARY

A patient who had polycythemia vera was given radioactive phosphorus and developed severe thrombocytopenic purpura associated with prominent changes in the appearance of the megakaryocytes.

It is suggested that radioactive phosphorus should be used with caution especially in patients who already have thrombocytopenia.

REFERENCES

1. HALL, B. E., WATKINS, C. H., HARGRAVES, M. M. and GIFFIN, H. Z. Radioactive phosphorus in the treatment of polycythemia vera. *Am. J. M. Sc.*, 209: 712, 1945.
2. HEMPELMAN, L. H., REINHARD, E. H., MOORE, C. V., BIERBAUM, O. S. and MOORE, S. Hematologic complications of therapy with radioactive phosphorus. *J. Lab. & Clin. Med.*, 29: 1020, 1944.

Foreword

DIABETES MELLITUS, for good reasons, has attracted the attention of outstanding investigators in many fields of medicine. In the first place, this disease is a health hazard of major significance. Data on the incidence of the disease have been published but for the most part are difficult to assess. A reasonable estimate, however, is that the population of the United States includes not less than 1,000,000 diabetic persons, and many have believed that the incidence of the disease has increased in recent years and may still be increasing.

For a long period we have kept a separate yearly count of the new cases of diabetes seen at the Mayo Clinic, and of the return patients treated for diabetes at some previous time in the clinic. We have related the number of new cases of diabetes year by year to the total number of new patients who registered for examination in the clinic in the corresponding years, arriving thus at a *new case rate index*. Admittedly, this index is not the literal equivalent of the incidence of the disease in, or the case rate of, the population. The latter could be obtained only if all cases of diabetes were detected and their number divided by the population, which up to now has not been possible. However, the index can be accepted as a reasonable barometer of changes in the case rate of the population because any important increase or decrease in the incidence of diabetes in any given year in the population from which are drawn the patients of the clinic very likely would be reflected in a corresponding change in the incidence of new diabetic patients coming to the clinic.

With this thought in mind, changes in the new case rate index over the years are worthy of notice. The index in 1920 was 0.62 per cent; it was 1.05 per cent in 1925; 1.24 per cent in 1930; 1.60 per cent in 1935 and 2 per cent in 1941. Since 1941 it has remained in the neighborhood of 2 per cent. In 1948 there were 1,375 new diabetic patients; of this number 329 had been seen in the clinic in earlier years but had not given evidence of diabetes at previous examinations. Of interest is the fact that the disease in 50.2 per cent of these new patients was severe enough to necessitate the use of insulin. Also of some significance is the fact that for every five new patients who knew they had diabetes when they came to the clinic, another instance of diabetes was discovered among patients in the clinic who when they registered had not suspected that they had diabetes.

The increase between 1920 and 1941 in the new case rate index for diabetes in the Mayo Clinic is not to be explained by the discovery of insulin in 1920 and the consequent increasing interest in the detection of diabetes. Relatively few of the patients who come to the clinic do so because of diabetes, and the reliability of the detection of diabetes in the clinic has not changed since 1920. For every patient registering since that year, and before, urinalysis has been performed and, with few exceptions, when glycosuria has been detected the level of blood sugar has been determined; a fasting blood sugar determination first and when uncertainty remained, a glucose tolerance test. The figures I have quoted relate only

to new patients for whom a diagnosis of diabetes mellitus was based on the finding of abnormally high blood sugar levels; therefore, from the data given the inference is clear that in the population from which the patients of the clinic are drawn the incidence of diabetes between 1920 and 1941 was multiplied by three or more, also that since 1941 there has been no further increase. The stabilization of the new case rate index since 1941 is reassuring; nevertheless, the incidence of diabetes obviously is of such magnitude as to call for major efforts in detecting the disease and in its treatment.

Another reason for the widespread interest in diabetes mellitus is that this disease affords unusual opportunities for study of the machinery of metabolism. It opens a door, so to speak, and thereby provides a view of what is going on inside. Dextro-rotatory glucose appears in the urine. The explanation came with von Mehring's and Minkowski's discovery in 1889 that ablation of the pancreas provoked diabetes. The interest thus aroused culminated in the separation of insulin from the pancreas by Banting and Best in 1920, and in the discovery by them of the usefulness of insulin in the treatment of experimental pancreatic diabetes and the diabetes mellitus of man.

Failure to utilize D-glucose, when the failure is severe, leads to accumulation in the body of aceto-acetic acid, hydroxybutyric acid and acetone. An alkali deficit results from this accumulation of organic acids. Study of the chemical disturbances which bring all this about has thrown some light on the normal metabolism of fats and proteins, and the long series of investigations of diabetic acidosis, initiated by Hallervorden, Stadelmann and Minkowski, students of Naunyn in Königsberg, Germany, in the 1880's, has resulted in the ever growing body of knowledge about this most immediate hazard of diabetes mellitus.

Finally, in more recent years some understanding has been gained of the parts played in the metabolism of carbohydrate by the pituitary and adrenal glands. This stems mainly from Houssay's and Biasotti's brilliant finding in 1930 that pancreatic diabetes could be modified profoundly by ablation of the pituitary gland. Most recently additional advance has been promoted through the isolation in relatively pure form of many of the hormones of the anterior lobe of the pituitary body and of the cortex of the adrenal gland.

In the symposium on diabetes mellitus which follows we are indebted to Dr. Stetten for a clear interpretation of current views about the fate of D-glucose in metabolism; to Dr. Haist for reviewing the contributions to knowledge of diabetes mellitus which have come from experimental diabetes; to Dr. Balfour and Dr. Sprague for clinical reports of cases of human diabetes in which endocrine glands other than the pancreatic islands were importantly involved; to Dr. White for sharing with us her large experience with the problem of pregnancy in diabetes; to Dr. Barach for his views on what now appears to be the major threat in diabetes, premature sclerosis of the vascular tree; to Dr. Wilder, Jr., for reflections on the problem presented to the non-specialists in diabetes who must assume responsibility for the care of a large proportion of the diabetic population; and finally to Dr. Guest for a discussion of procedures currently employed in treating diabetic acidosis.

The subjects covered in these papers are in fields which at present are undergoing energetic cultivation. The material, much of it at least, is not as yet in textbooks. The purpose back of this symposium is to bring us up to date in these several major aspects of diabetes mellitus.

RUSSELL M. WILDER, M.D.

Symposium on Diabetes Mellitus

Carbohydrate Metabolism*

DEWITT STETTEN, JR., M.D.

New York, New York

ENERGY CONSIDERATIONS

MANY of the individual processes which, when taken together comprise the normal body economy, when considered as isolated systems prove to be endergonic, that is, energy-consuming processes, incapable of continued operation unless the needed energy is supplied in one or another fashion. By way of preface to a discussion of the role of carbohydrates in the total mammalian metabolism it may be well to tabulate some of these endergonic processes in order that insight may be gained into the disposition of the relatively enormous amounts of energy that the normal organism derives from the breakdown of carbohydrates each day: (a) the maintenance of body temperature at a level in general above that of the environment, (b) the performance of mechanical work, both voluntary and involuntary, incident to muscle contraction, (c) the initiation and transmission of neural impulses, (d) the secretion or reabsorption of tissue and blood constituents, often against a concentration gradient, and (e) the continuous regeneration of the large molecules of protein, polysaccharide and fat, which make up the major portion of the organic components of protoplasm, for the synthesis of which not only the small building stones but also a supply of energy is needed.

These and other processes are continuously consuming energy, and this energy deficit must ultimately be met by the caloric supply of the diet if the organism is to remain in balance. The incidental energy requirements of growth, pregnancy, lactation, tissue repair and wound healing must

also be derived from this source, and in view of the fact that in a perfectly normal dietary well over half of the calories of the diet may appear in the form of carbohydrate, it is of obvious importance to understand what little is known of the means whereby the energy, made available to the organism by the breakdown of carbohydrate, is delivered to these various energy-consuming processes.

The primitive idea that sugar is burned in the animal body as it might be burned in a furnace and that the heat liberated thereby is the source of energy for muscle work has long been recognized as untenable. The efficiency of the transfer of usable energy through the mode of heat is

limited by the fraction $\frac{\text{temperature difference}}{\text{absolute temperature}}$

and such processes become efficient only when a large temperature difference can be achieved. Thus, at body temperature, assuming a thermal difference of 10°C to occur, no more than one thirtieth of the energy liberated by the combustion of sugar would be available for the performance of useful work. Yet isolated muscle has been shown to operate on a nutrient of glucose with vastly greater efficiency than 3 per cent despite the fact that no significant thermal differences within the muscle have been shown to occur. From this it follows that a large portion of the energy liberated by the breakdown of glucose in the mammalian cell must be delivered to systems capable of accepting energy and transforming it into useful work without the intervention of the energy-mode of heat. Recognition of this fact gave rise to the concept of "energy-linked processes" wherein

* From the Division of Nutrition and Physiology, The Public Health Research Institute of The City of New York, Inc., N. Y.

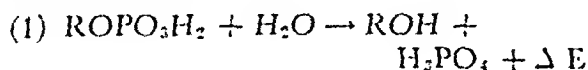
the energy released by one reaction is immediately accepted and utilized by some other reaction occurring simultaneously. After a generation of exploration one may now point to one such energy link, which has clearly been proved to be operative in

TYPES OF COMPOUNDS OF PHOSPHORIC ACID

Type	Structure	Energy of Hydrolysis	Examples
Phosphoric ester of simple alcohol	$\begin{array}{c} \text{H} \quad \text{R} \\ \quad \\ \text{C}-\text{C}-\text{O}-\text{P} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{O} \\ \searrow \text{OH} \end{array} \\ \\ \text{H} \end{array}$	Low	Glucose-6-phosphate, 3-phosphoglyceraldehyde, 2-phosphoglyceric acid
Phosphoric acid acetal	$\begin{array}{c} \text{O} \\ \\ \text{C}-\text{C}-\text{O}-\text{P} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{O} \\ \searrow \text{OH} \end{array} \\ \\ \text{H} \end{array}$	Low	Glucose-1-phosphate, 1,3-diphosphoglyceric aldehyde (the 1-phosphate)
Anhydride of phosphoric acid	$\begin{array}{c} \text{O} \quad \text{O} \\ \quad \\ \text{O}-\text{P}-\text{O}-\text{P} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{O} \\ \searrow \text{OH} \end{array} \\ \\ \text{OH} \end{array}$	High	Adenosine triphosphate, adenosine diphosphate
Mixed anhydride of phosphoric acid	$\begin{array}{c} \text{O} \quad \text{O} \\ \quad \\ \text{C}-\text{C}-\text{O}-\text{P} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{O} \\ \searrow \text{OH} \end{array} \\ \\ \text{H} \end{array}$	High	Acetyl phosphate, 1,3-diphosphoglyceric acid (the 1-phosphate)
Enol phosphate	$\begin{array}{c} \text{C}=\text{C}-\text{O}-\text{P} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{O} \\ \searrow \text{OH} \end{array} \\ \\ \text{R} \end{array}$	High	Phosphopyruvic acid
N-substituted phosphinic acid	$\begin{array}{c} \text{OH} \\ \\ -\text{C}-\text{N}-\text{P} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{O} \\ \searrow \text{OH} \end{array} \\ \\ \text{H} \end{array}$	High	Phosphocreatine, phosphoarginine

biologic systems and which must serve as an example of the devices which have evolved to accomplish the necessary energy transfer.

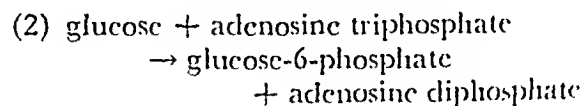
The biologically important compounds of phosphoric acid¹ have been shown to fall roughly into two groups, and this division is based on the amount of energy which is released when these compounds are subjected to hydrolysis. If one considers the reaction type:



where ΔE is the energy released, one sees that of some compounds of phosphoric acid, the quantity ΔE is small, and, intimately associated with this fact, the hydrolysis as

written is readily reversible and the possibility exists that the compound may arise and accumulate to an appreciable extent as a result of spontaneous synthesis from its parts. Such compounds are said to contain "low energy phosphate." There are, on the other hand, numerous compounds of phosphoric acid which, when subjected to hydrolysis, yield large amounts of energy; in regard to the foregoing equation, ΔE is a large quantity. The hydrolysis of such compounds proceeds essentially irreversibly and completely, and such compounds cannot be pictured as arising to any appreciable extent from spontaneous interaction of the products of hydrolysis. These compounds are referred to as "high-energy phosphate" compounds.

Included in the table are examples of these two types of compounds of phosphoric acid. In relation to this table, it should be pointed out that it is thermodynamically possible for any compound of high energy to surrender its phosphate residue to some acceptor and generate a phospho-compound of low energy, whereas the reverse cannot occur. An example of a reaction of this type is the well known hexokinase-catalyzed phosphorylation of glucose:



Here a low-energy phosphate bond has been established at the expense of a high-energy bond.

Of the several high energy compounds listed in the table, by way of generalization it may be stated that the energies of hydrolysis of all of these compounds are of the same order of magnitude. This fact gives rise to the thermodynamic possibility of the generation of a new high energy phosphate bond at the expense of another high energy bond, and, furthermore, since the net gain or loss of energy in such a reaction will be small, such a reaction may be expected to proceed reversibly. Examples are given herewith:

- (3) phosphopyruvic acid
+ adenosine diphosphate \rightleftharpoons pyruvic acid
+ adenosine triphosphate
- (4) phosphocreatine
+ adenosine diphosphate \rightleftharpoons creatine
+ adenosine triphosphate

The energy link believed to intervene between the catabolism of glucose, on the one hand, and the contraction of muscle, on the other, is closely related to such shuttling about of high energy phosphate. The current picture describes the contractile unit of the myofibril as existing in two states, an extended and a contracted state. In the extended or elongated condition, it is rich in potential energy, like an extended spring. As it contracts, with the generation of kinetic energy, it loses potential energy, precisely as is the case with a stretched spring that is permitted to contract, and before it can do any more work, it must be recharged with energy and reconverted to the extended condition. This transformation is apparently accompanied with and closely related to the introduction, into the myosin unit, of phosphate, and, what is of importance to the present discussion, the phosphate required is of the high energy variety. The continuous operation of a muscle fiber may be pictured as being made up of two alternating phases: extension, accompanied by an increase in potential energy and the coincident introduction of high energy phosphate at the expense of some high energy phosphate compound in the vicinity; and contraction, accompanied by the performance of mechanical work on the environment, release of kinetic energy, decrease in potential energy and loss of phosphate as inorganic phosphate ions at an energy level of 0. Such a process may be repeated continuously as long as there is a supply of compounds of phosphoric acid of the energy-rich variety available in the neighborhood; in muscle tissue such a reservoir is at hand (Fig. 1). The terminal phosphoric acid residue of adenosine triphosphate appears to be the immediate source of high energy phosphate for the

recharging of the contracted myofibril. Backing up this reservoir there is a second reservoir, in the form of the creatine phosphate which is abundant in striated muscle. By virtue of these reservoirs an isolated muscle may be made to undergo repeated

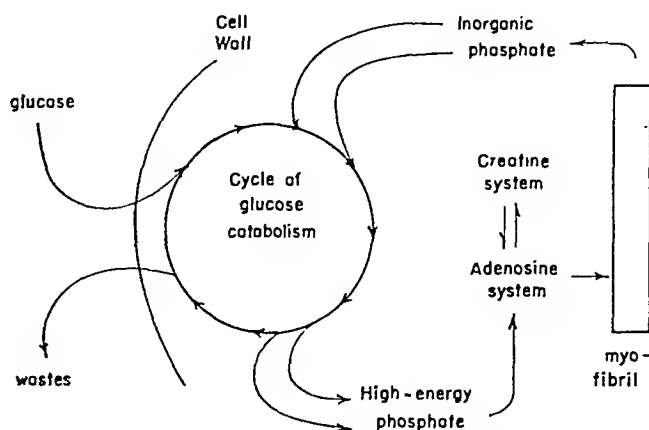


FIG. 1. The role of high energy phosphate in the transfer of energy from glucose catabolism to effector organ. (Adapted from Lipmann, F. In Nord, F. F. and Werkman, C. H. *Advances in Enzymology*. Vol. 1, p. 122, 1941.).

contractions even though carbohydrate catabolism may have been completely inhibited by the use of suitable poisons. Inevitably, however, in such a preparation, these reservoirs of high energy phosphate will soon be depleted, the high energy phosphate necessary to recharge the myofibrils will no longer be available and muscle work will come to a standstill.

It is at this point that the role of glucose catabolism in the working cell must be taken into account. One of the important consequences of the breakdown of glucose in the living cell is the generation of new high energy phosphate compounds in the formation of which glucose is catabolized and inorganic phosphate ions are consumed. Examples of individual reactions in which such high energy phosphate compounds arise will be given later in the text. Suffice it to state at this point that, per molecule of glucose degraded to pyruvate or lactate, two high energy phosphate bonds, according to current understanding, will have been created *de novo*. As the high energy phosphate which arises incident to the breakdown of glucose is transferable to

adenosine diphosphate, to regenerate adenosine triphosphate and secondarily creatine phosphate, the processes of normal glucose catabolism tend to offset the depletion of high energy phosphate stores that would otherwise result from continued muscle work.

This energy link between the breakdown of glucose and the performance of muscle work, involving the repeated generation and destruction of high energy phosphate, must not be supposed to be peculiar to this system. Indeed, at least one other endergonic process, the generation of polysaccharides, has been shown to be linked energetically to glucose breakdown through the same type of shuttling about of phosphate residues (discussed later), and it may be supposed that other energy-consuming processes operate, in the cell which is destroying glucose, by virtue of this same energy link. It must, however, be borne in mind that energy links in addition to the one described may yet be unearthed, and, indeed, at the present time one is able, by reactions known to occur, to account for the disposition of only a small fraction of the energy liberated in the complete oxidation of glucose to carbon dioxide and water.

SOURCES OF GLUCOSE

The glucose on which the cells of the mammalian organism depend, to a greater or lesser extent, for their continued nutrition is of course the glucose dissolved in the extracellular fluids of the body, of which the blood plasma may be taken as representative. Whereas it is undoubtedly true that some mammalian cells retain a vestigial capacity to assimilate carbon dioxide,² the mammal is obviously incapable of synthesizing its full supplement of glucose from carbon dioxide and water, a synthesis that is effectively carried out by certain microorganisms and chlorophyll-containing plants. There are three sources of blood glucose that come into consideration, and of these the most important one quantitatively is the carbohydrate of the diet. The other contributions to the blood glucose

may be classified under the headings of glycogenolysis and gluconeogenesis.

The carbohydrates of the diet that are of nutritional significance are surprisingly few in number (Fig. 2). Only three monosaccharides, glucose, fructose and galactose, need be mentioned, and although the first two of these do occur as such in various fruits, it is questionable whether any of these three ever comprises a major portion of a normal diet. Of the disaccharides, sucrose, the common sugar of cane and beet, is of course a variable dietary component, and lactose, the carbohydrate of milk, is obviously of significance in infant nutrition. Maltose is of interest not so much as a naturally occurring product but rather as an intermediate in the breakdown of larger polysaccharide molecules. The hydrolysis of each of these disaccharides gives rise to a pair of monosaccharide molecules:

- (5) sucrose \rightarrow glucose + fructose
- (6) lactose \rightarrow glucose + galactose
- (7) maltose \rightarrow glucose + glucose

The major portion of the usual dietary carbohydrate is made up of polysaccharides, compounds of large and imperfectly known molecular size. The starches, of vegetable origin, and glycogen, of animal origin, are the important members of this group, and both are made up of glucose fragments linked to each other in what is termed "glucosidic linkage," in which the number 1 carbon of one glucose unit is coupled, through an oxygen bridge, to the number 4 or number 6 carbon of an adjacent glucose unit. On complete hydrolysis of these materials the sole carbohydrate obtained is glucose.

The remaining carbohydrates of the diet are of little nutritional importance. The pentoses, such as xylose and arabinose, which may be present in the diet to a scant extent, are known to be absorbed across the intestinal mucosa much more slowly than the common hexoses, and little is known of their further metabolic utilization. Polysaccharides which on hydrolysis yield pentoses are represented among the gums, such

as gum arabic and acacia, as well as agar, but these are not digested or absorbed and serve merely to increase the bulk of the intestinal contents. Similarly cellulose, a polysaccharide of glucose, although apparently digested by certain ruminants, is not

of digestion accomplished by this enzyme is probably small. When the bolus of food enters the stomach, ptyalin is rapidly inactivated by the acidic environment which it encounters, so that enzymic digestion comes to a standstill. A small degree

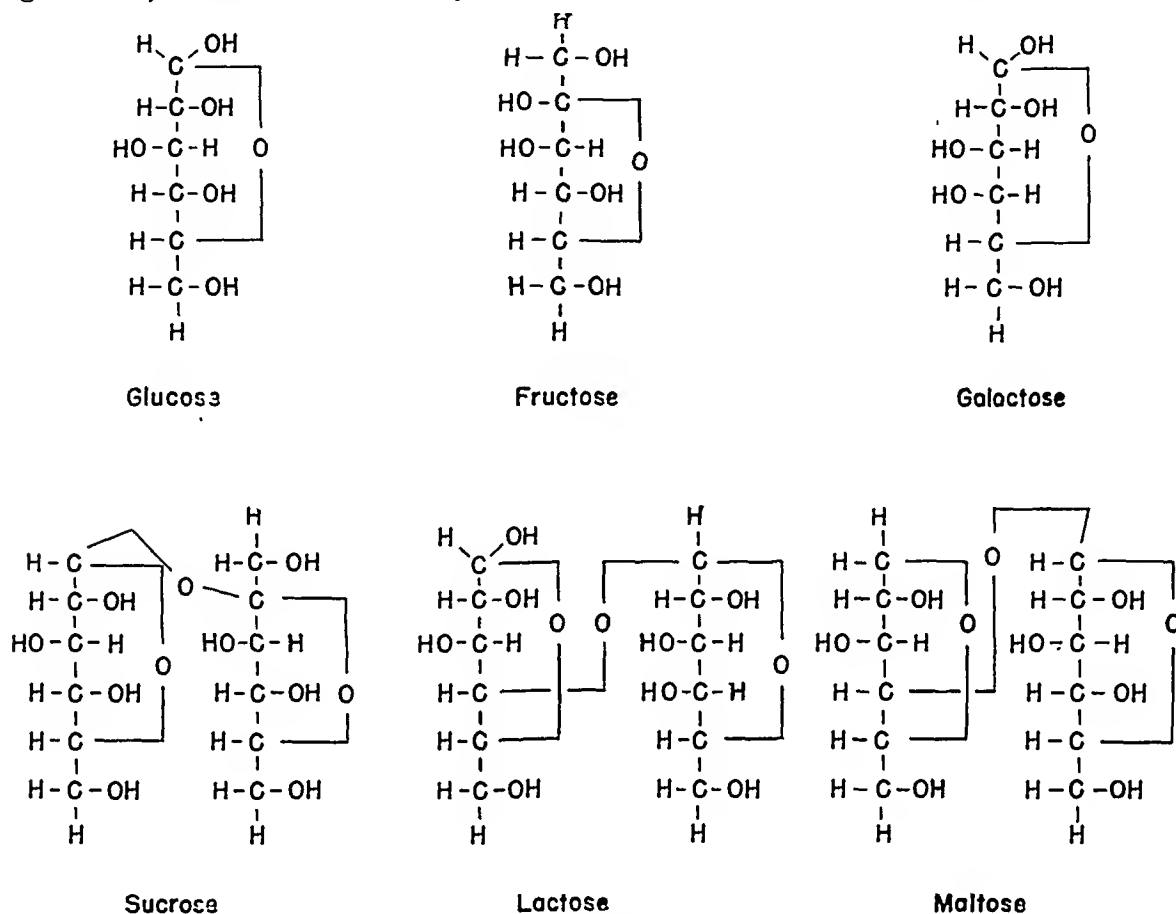


FIG. 2. Formulas of the nutritionally important sugars.

subject to digestion in the human gastrointestinal tract and serves only as roughage.

The digestion of carbohydrates, like the digestion of proteins and fats, may be described as a series of enzyme-catalyzed hydrolyses in which the large molecules of the diet are broken down to smaller unit fragments preparatory to their absorption. It is generally believed that the bulk of dietary carbohydrate is degraded to the monosaccharide level prior to absorption, although small amounts of disaccharide, such as sucrose, may be absorbed without hydrolysis. The first of the enzymes, in the most general sense glucosidases, to operate on ingested polysaccharide is the salivary amylase, ptyalin. In view of the short duration of contact between dietary polysaccharide and active ptyalin, the extent

of digestion in the stomach incident to the catalysis of hydrogen ions has been postulated.

The small intestine is the major site both of polysaccharide digestion and of absorption of the resultant simple sugars. Pancreatic amylase and the glucosidases of the succus entericus both participate in catalyzing the hydrolysis of glucosidic links and the ultimate disintegration of the complex sugars of the diet to the monosaccharide level.

Derived from the carbohydrates of the diet one may expect to see in the lumen of the small intestine a mixture of glucose, fructose and galactose, and, except for that portion which undergoes bacterial fermentation, these monosaccharides are delivered to the portal bloodstream in a quantitative

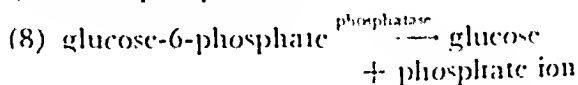
fashion. The transport of these hexose molecules across the intestinal mucosa appears not to be simply a matter of diffusion, since the rate of this transport is in general independent of the concentration gradient against which it is operating. It appears to be a vital process, dependent in some fashion on the reaction of phosphorylation and probably is not dissimilar to the process of reabsorption of glucose from the renal tubule. The several sugars are absorbed from the intestinal canal at widely differing rates, the order of these rates being: galactose > glucose > fructose > mannose > pentoses.³

Glucose is certainly the most abundant hexose entering the bloodstream from the intestinal tract. Galactose and fructose, insofar as they are absorbed and enter the processes of glycolysis and glycogenesis, may be presumed to be capable of ready transformation into the glucose configuration. Of the various monosaccharides of metabolic interest, galactose is formed abundantly and excreted as lactose in the process of lactation and also crops up as the characteristic sugar in many cerebro-sides; ribose and desoxyribose are formed from unknown precursors in the body and appear in the nucleic acids and nucleotides, and xyloketose appears as a urinary constituent in pentosuria. From the nutritional point of view, however, the concern is predominantly with glucose.

In addition to the absorption of the products of carbohydrate digestion from the intestinal canal, there are two other types of processes which contribute to the blood glucose, and these are conveniently discussed under the headings of gluconeogenesis and glycogenolysis. Under the term gluconeogenesis may be included all reactions which originate with noncarbohydrate precursors and terminate with the generation of glucose. Among the materials which the body is capable of employing in this fashion are: (a) essentially all of the products that the body can generate from glucose down to and including the four-carbon dicarboxylic acids, (b) all of the

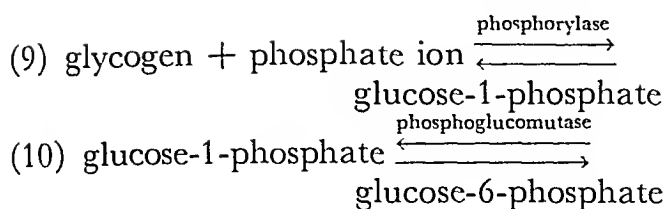
amino acids that are capable of being transformed into or of contributing carbon atoms to any of the foregoing intermediates—such amino acids comprise the glucogenic amino acids—and (c) certainly glycerol and, according to some authorities, possibly the fatty acids, which may arise from the hydrolysis of fat.

Since, in general, the reactions of glycolysis, glucose breakdown, may proceed in both directions in the body, the products of glycolysis would be expected to be glucogenic. Certain of these products, however, may arise from other sources. Thus, α -ketoglutaric acid may be formed from glutamic acid and presumably from the other five-carbon amino acids as well, and oxaloacetic acid can certainly arise from the amino acid aspartic acid. The three-carbon amino acids, alanine, serine and cysteine may contribute their carbon skeletons to form pyruvic acid, and glycerol is similarly interconvertible in the body with certain of the three-carbon fragments that arise from the breakdown of glucose. When proceeding in the direction of glucose formation, these processes all funnel into the formation of glucose-6-phosphate. This compound, in common with other phosphorylated compounds, appears to cross cell membranes slowly, if at all, and is believed to be utilized for the most part in the very cells in which it is formed. The enzyme required for the catalysis of the irreversible hydrolysis of this product, perhaps a specific glucose-6-phosphatase;^{3a}



appears not to be uniformly distributed, and, while it is abundantly present in liver, it is lacking in striated muscle. Thus, whereas the liver is well able to contribute to the blood glucose as a result of gluconeogenic processes, such processes in muscle result in the augmentation of some other product, notably glycogen.

The third source of blood glucose to be considered is the breakdown of glycogen. This proceeds over well recognized steps:⁴



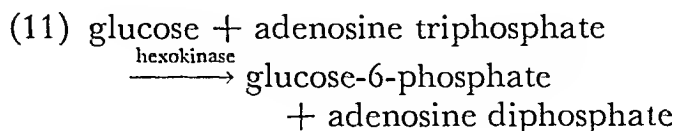
The glucose-6-phosphate which arises as a result of these reactions is, of course, subject to the same restrictions described, in that in liver, but not in muscle, it may be hydrolyzed to yield glucose (reaction 8). A consequence of this enzymic deficiency of striated muscle is the fact that muscle glycogen cannot contribute directly to the blood glucose, that the first products of glycogen breakdown in muscle that can escape readily from the muscle cell are pyruvic and lactic acids and that only as these do escape and are captured by the liver and employed there for gluconeogenesis can muscle glycogen contribute to the glucose of the blood.

GLYCOLYSIS

In summing up the sources of blood glucose, it may be pointed out that, in a quantitative sense, the breakdown of glycogen constitutes a much smaller contribution than do the other two processes and appears to be of major importance only in times of acute stress. It should also be stressed that all three processes are undoubtedly operating continuously in the normal subject and this leads to a consideration of the fate, in the animal body, of the glucose thus made available. In the normal subject, essentially all of this glucose is consumed in one way or another, no appreciable amounts appearing in the excreta. Many metabolic pathways and many hypothetic intermediates have at one time or another come into consideration. The pathways and the intermediates presented herewith are those currently acceptable and well established experimentally, but should not be construed as the only possible routes over which glucose can be utilized. Rather should this scheme be considered as a highly probable series of reactions, which is believed to occur, with

relatively minor modifications, in widely divergent types of cells, and which may serve as a model of the manner in which glucose is catabolized.⁵

The first step in the series (Fig. 3) appears to be the formation of glucose-6-phosphate from glucose by the irreversible, exergonic reaction:



It should be particularly noted that this reaction is not the reversal of the reaction whereby glucose-6-phosphate is hydrolyzed to glucose (reaction 8). The enzyme catalyzing the present reaction, in contrast to the phosphatase mentioned previously, appears to be ubiquitous, and this, the hexokinase reaction, would seem to occur in essentially all living cells. An important consequence of this reaction is that it converts the freely diffusing glucose into a phosphate which crosses membranes with difficulty and is thereby pictured as serving to capture glucose molecules in the intracellular compartment.⁶ It has been suggested that it is by virtue of this mechanism of capture of glucose that the cells of the mammalian body are able to thrive on a predominantly glucose nutrient in spite of the fact that the concentration of glucose in the extracellular space is relatively low, in the neighborhood of 0.1 per cent.

Three possible fates of glucose-6-phosphate must next be considered. In the liver, but not in muscle, it may be hydrolyzed back to glucose by the action of phosphatase (reaction 8). Again, by the reversal of reaction 10 it may be transformed into glucose-1-phosphate, and from this product a wide variety of cells are able to form glycogen. This latter reaction has been shown to require the same phosphorylase which was involved in the breakdown of glycogen (reaction 9) and, in addition, a small seed of glycogen or some similar polysaccharide to initiate the coupling of one glucose fragment to another. In the course of this

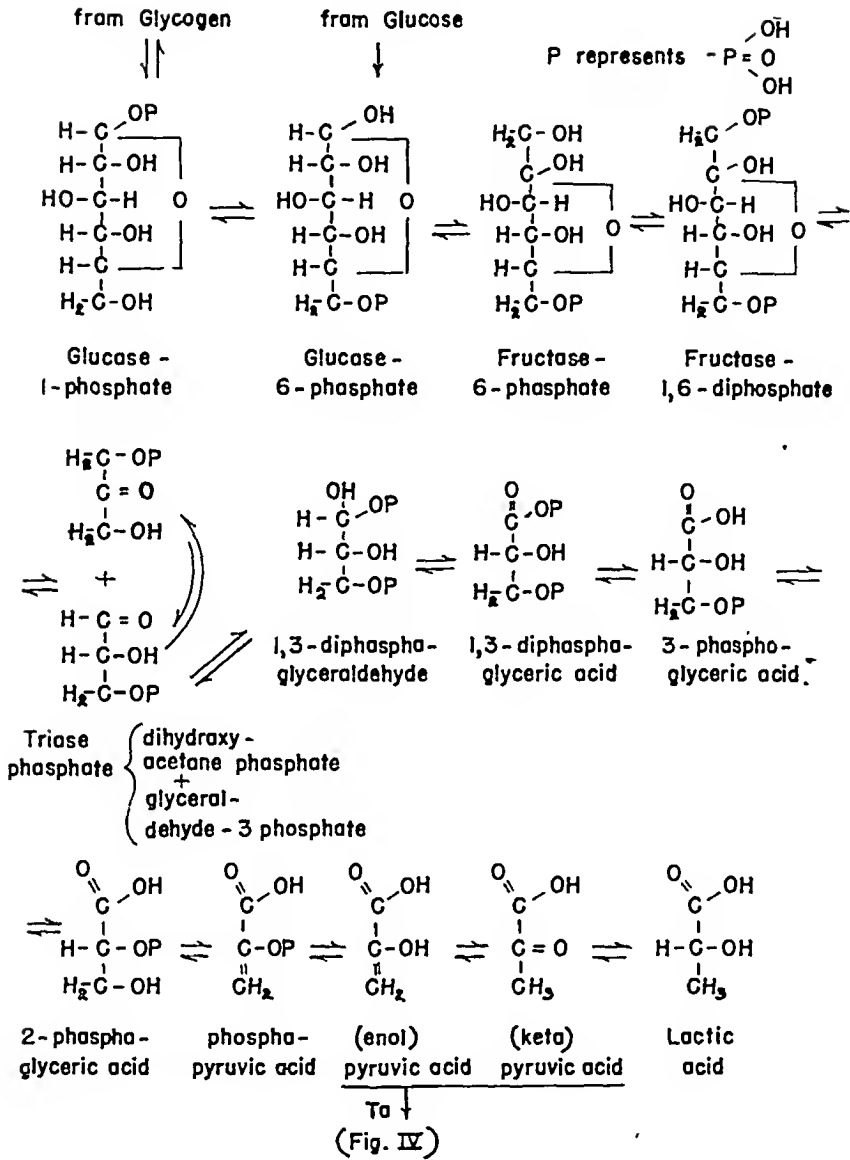
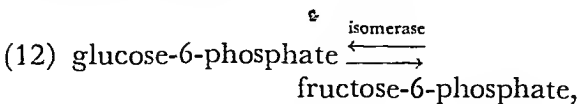
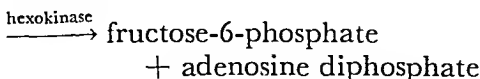
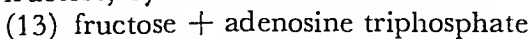


FIG. 3. The pathway of anaerobic glycolysis.

reaction phosphate ion is eliminated. The third fate of glucose-6-phosphate is its transformation to fructose-6-phosphate, a reversible reaction:

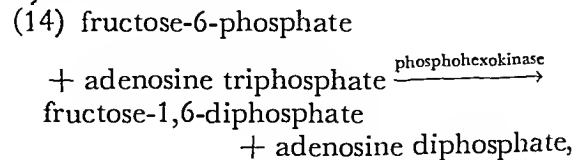


and since the same product may arise from fructose, by the reaction:



it may be considered that it is at this point that the metabolisms of glucose and of fructose merge.

Fructose-6-phosphate now acquires a second phosphate in the number 1 position by the reaction:



and the resulting product, loaded at both ends, undergoes cleavage at the midpoint to yield a mixture of the two triose phosphates:

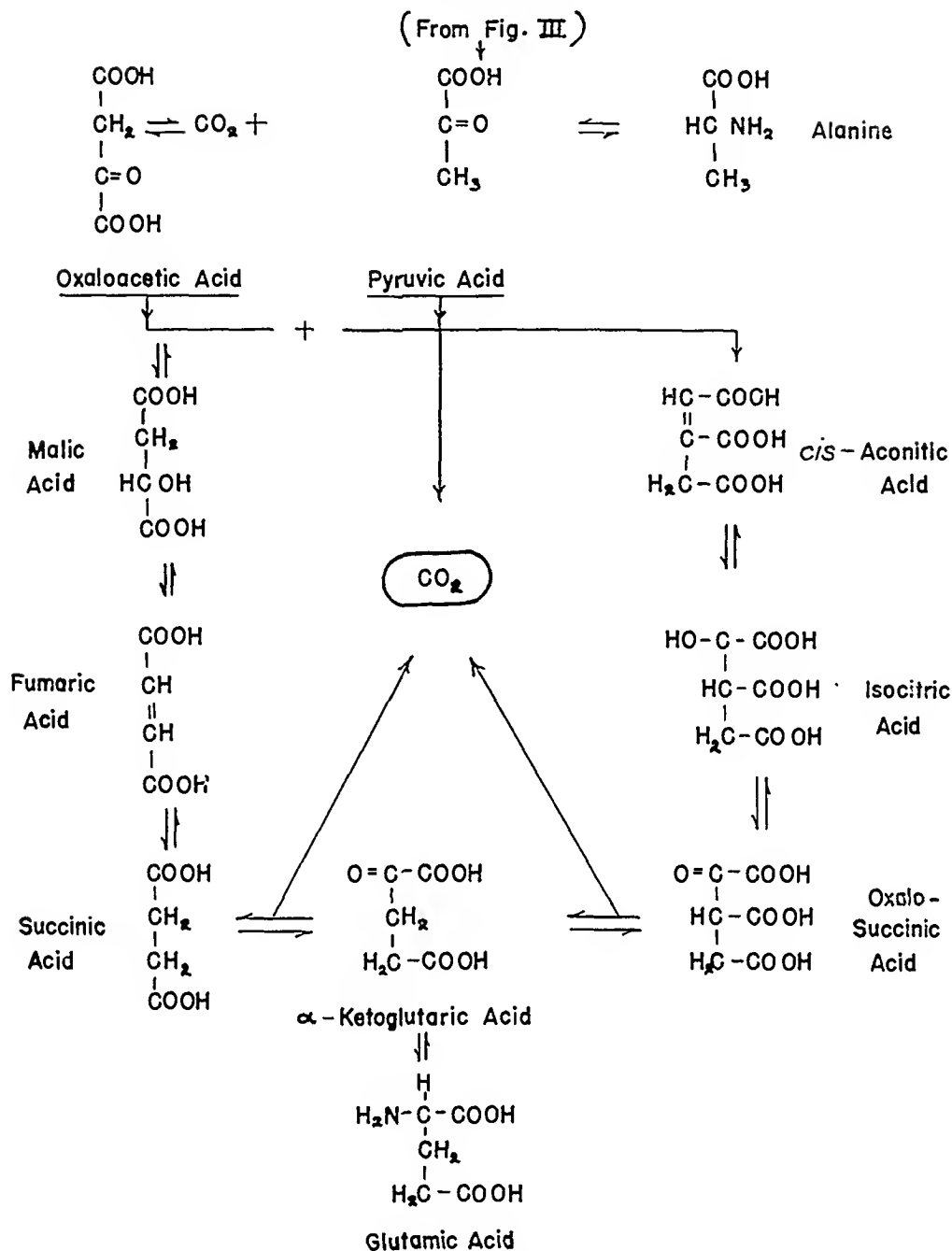


FIG. 4. The oxidation of pyruvic acid.

- (15) fructose-1,6-diphosphate $\xrightleftharpoons{\text{zymohexase}}$ glyceraldehyde-3-phosphate + dihydroxyacetone phosphate.

These two isomeric compounds form an equilibrium mixture in that they are biologically interconvertible:

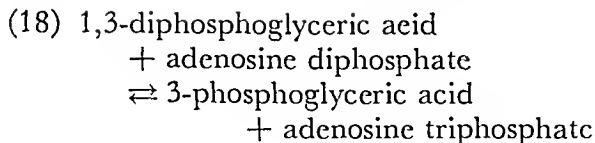
- (16) dihydroxyacetone phosphate $\xrightleftharpoons{\text{triose isomerase}}$ glyceraldehyde-3-phosphate.

Glyceraldehyde-3-phosphate next undergoes spontaneous reaction with inorganic phosphate to yield glyceraldehyde-1,3-diphosphate. It should be noted that the

phosphate bond thus established is of the low energy variety (table). When this compound is oxidized by the transfer of hydrogen to coenzyme I:

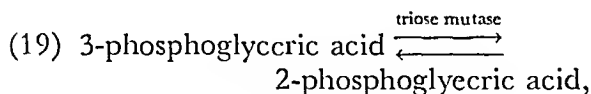
- (17) glyceraldehyde-1,3-diphosphate + coenzyme 1 (ox.) \rightleftharpoons 1,3-diphosphoglyceric acid + coenzyme 1 (red.),

the phosphate in position 1 is transformed from a low energy phosphoric acid acetal into a high energy mixed anhydride of phosphoric acid (table), capable of delivery to other high energy systems:

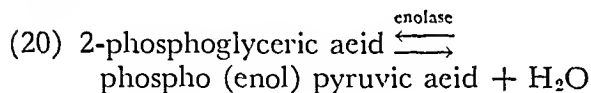


The last three reactions have in effect augmented the energy level of inorganic phosphate, initially zero, up to an energy level sufficiently high to permit of the regeneration of high energy adenosine triphosphate, the energy in this case derived from the energy of oxidation of an aldehyde up to the level of a carboxy acid.

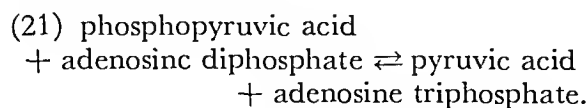
The rearrangement of 3-phosphoglyceric acid according to the reaction:



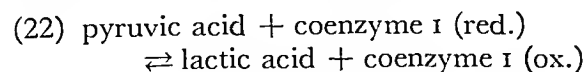
is followed by the dehydration of this product:



In this reaction once again one sees the augmentation of energy level in a phosphate bond. In the starting material, phosphate occurs as an ester of a secondary alcohol, at low energy level, whereas in the product, phosphate is present as a high energy enol ester (table). The regeneration of another mol of adenosine triphosphate is thus made possible, at the expense of the energy yielded by glycolysis, as is seen in the next reaction of the series:

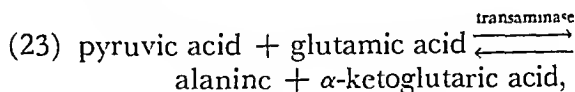


The possible fates of pyruvic acid (Fig. 4) which, in alkaline solution, exists as an equilibrium mixture of the enol and keto forms, are several.⁷ Under conditions of oxygen lack, when the several coenzymes of the hydrogen transport system are largely in the reduced state, the reaction:



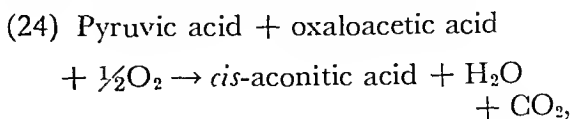
may be expected to proceed to the right to an appreciable extent, and in these circumstances, since lactic acid appears to have no pathway open to it other than excretion or reoxidation to pyruvic acid, lactic acid may be expected to accumulate in the body fluids. It may be pointed out that lactic acid ($\text{C}_3\text{H}_6\text{O}_3$) is grossly at the same level of oxidation as glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) and that in the reactions described thus far, there is neither an over-all consumption of oxygen nor a liberation of carbon dioxide. In fact all these reactions do run, in many circumstances, completely anaerobically. Lactic acid accumulating as glucose disappears. In general, however, when oxygen is abundantly supplied, pyruvic acid is drained into other channels and the equilibrium of reaction 22 is shifted to the left.

Another possible disposition of pyruvic acid is its conversion to alanine by the transfer of an amino group from some other amino acid:



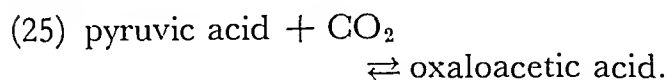
a reaction for which pyridoxal phosphate has been shown to serve as a coenzyme.

Yet another fate of pyruvic acid is today supposed to entail a preliminary degradation to an as yet unidentified two-carbon fragment, sometimes referred to as "acetyl," and condensation of this product with oxaloacetic acid to yield *cis*-aconitic acid. In order to balance the over-all reaction:

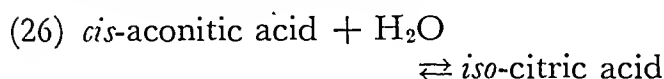


it will be noted that oxygen is required among the reactants and carbon dioxide occurs among the products. This reaction, which initiates the so-called "tricarboxylic acid cycle," may be taken as the first individual reaction which is necessarily aerobic. A coenzyme necessary for this, and indeed several other reactions of pyruvic acid, is thiamine pyrophosphate, and the increase in blood and urine pyruvate levels

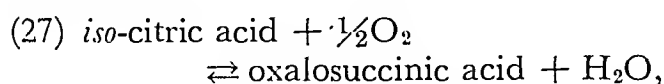
in thiamine deficient states has been ascribed to inhibition of this reaction. It is noteworthy that the other reagent required for this disposition of pyruvic acid, oxaloacetic acid, may in turn arise from pyruvic acid:



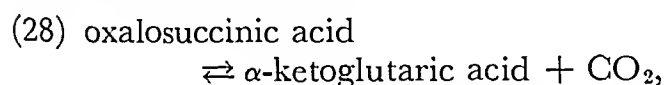
The hydration of *cis*-aconitate:



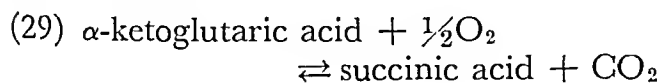
is followed by its dehydrogenation:



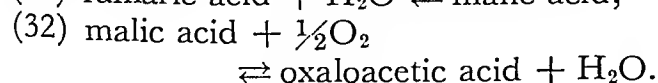
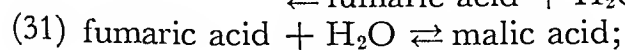
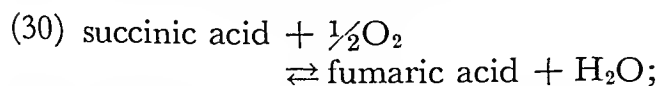
and here again, to balance the over-all reaction, oxygen is required. Oxalosuccinic acid now undergoes decarboxylation:



eliminating a second mol of carbon dioxide. The α -ketoglutaric acid thus formed may, by acceptance of an amino group, be transformed into glutamic acid. It may, on the other hand, undergo oxidative decarboxylation:



Three mols of carbon dioxide have now been eliminated, corresponding to the three carbon atoms of the pyruvic acid with which this, the aerobic phase, was initiated. The remaining reactions of the cycle, now called the "dicarboxylic acid cycle," may be pictured as serving to regenerate, from succinic acid, oxaloacetic acid:



Oxaloacetic acid is thus conserved and may react with another molecule of pyruvic acid in a cyclic fashion. It may, in addition, accept an amino group to yield aspartic

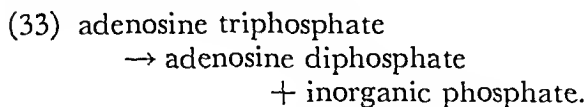
acid. Three of the keto acids which arise in the course of glucose catabolism, pyruvic, α -ketoglutaric and oxaloacetic, may readily and reversibly be converted into amino acids, and, in this fashion, a fusion of the metabolic pathways of proteins and carbohydrates is effected. At some point as yet undefined in the series below pyruvic acid, probably at the level of the two-carbon "acetyl fragment," a similar fusion of pathways of carbohydrate and fatty acid metabolism occurs whereby the over-all conversion of glucose to fatty acid takes place, on the one hand, and the products of fatty acid degradation feed into the tricarboxylic acid cycle, on the other.

Perhaps the most striking fact about this series of reactions is the occurrence of numerous individual steps whereby energy is released in small packages, rather than all at once in an explosive fashion. This gradual release of energy permits of its more efficient utilization in the endergonic processes of the body, and certain of the energy links that occur as glucose is degraded to pyruvate have been described. It should be pointed out, however, that the yield in energy as glucose is converted to pyruvate is far less than the yield obtained when pyruvate is further degraded to carbon dioxide, and of the energy links operating in this, the oxidative phase, little is known.

MAINTENANCE OF BLOOD GLUCOSE

For the cells of the body to carry out these reactions on glucose, a certain minimum concentration of glucose in the extracellular fluid must be maintained. One of the important mechanisms operating in this direction is the kidney, which normally prevents the loss of significant quantities of glucose in the urine as long as the level of blood glucose is below the threshold value. This is accomplished by the more or less quantitative reabsorption of glucose from the glomerular filtrate, a process in which the tubule cells transport at least a portion of the glucose against a concentration gradient. Such transport cannot be ac-

counted for on the basis of simple diffusion and necessarily consumes energy, and in view of the fact that such "up-hill" transport of glucose operates not only at the renal tubule but also at the intestinal mucosa and possibly elsewhere, it may be well to consider whence the necessary energy may arise. The sequence of events may be pictured as follows: Glucose diffuses across the barrier separating the lumen from the contents of the tubule cell; once in the cell it is phosphorylated according to reaction 11, which, in effect, disturbs the equilibrium in favor of diffusion of glucose into the cell from the lumen. Whereas glucose-6-phosphate does not escape from the cell, it may be pictured as circulating in the cytoplasm of the cell and coming in contact with a phosphatase which effects an irreversible hydrolysis according to reaction 8. A high concentration of glucose may thus be built up locally, and glucose may then diffuse from the intracellular fluid into the bloodstream. To compute the energy which would be expended by such a sequence of events, one has merely to add reactions 8 and 11, the sum being:



In other words, to transport one molecule of glucose against a concentration gradient by this means entails the loss of one high energy phosphate bond. That some such mechanism is operating at the renal tubule is indicated by the fact that phlorhizin, a known poison of phosphorylating systems, decidedly inhibits the tubular reabsorption of glucose.

Factors other than renal activity which serve to maintain the blood glucose at normal levels may conveniently be considered with reference to the endocrines which control these factors. Thus, the effect of epinephrine on carbohydrate metabolism may be assigned to an enhancement of the conversion of glycogen to glucose-6-phosphate (reactions 9 and 10). In the well nourished animal, with ample hepatic

glycogen, the major effect observed is a decrease in the quantity of glycogen of the liver and an increase in the quantity of blood glucose, arising from the ready hydrolysis of glucose-6-phosphate in the liver (reaction 8). In the previously fasted animal, however, in which the glycogen of the liver is depleted, the injection of epinephrine is followed by a decrease in glycogen of the muscle. At this site, however, glucose-6-phosphate cannot be hydrolyzed, and the glucose-6-phosphate therefore follows the path of anaerobic glycolysis (reactions 12 through 22) and the resulting lactic acid escapes into the bloodstream. The depleted liver captures a fraction of this lactic acid, which it may then convert into glycogen.

The anterior pituitary gland produces a specific inhibitor of the enzyme hexokinase (reaction 11).⁸ It appears to operate predominantly on the hexokinase of muscle and liver cells, and has little or no effect on the hexokinase contained in the cells of the central nervous system, the renal tubule or the intestinal mucosa. Since the hexokinase-catalyzed phosphorylation of glucose is, in a sense, a key reaction in the utilization of glucose, the presence of an excess of this inhibitor would be expected to interfere with the utilization of glucose, especially in muscle and in liver. A retardation in the formation of glucose-6-phosphate at these sites will result in an impairment of the utilization of glucose by these tissues as well as a decrease in the formation of all the substances which these tissues normally generate from glucose, among others, lactic and pyruvic acids, glycogen, fatty acids and carbon dioxide.

One of the actions of the secretion of the adrenal cortex appears to be an enhancement and prolongation of the action of this pituitary hexokinase inhibitor. When present in excess, essentially the same effects on the utilization of glucose by muscle and liver may be anticipated. The oxygenated steroids of the adrenal cortex are believed to have another effect on carbohydrate metabolism, namely, they are supposed to

favor gluconeogenesis at the expense of glucogenic amino acids of the proteins of the body. Both of these actions of the adrenal cortex will operate to increase the level of blood glucose, the one by impeding utilization and the other by favoring glucose synthesis.

An important action of insulin lies in its antagonism to the action of the inhibitor of hexokinase. Whereas insulin has no effect on hexokinase itself, it does serve to release this enzyme from the inhibition imposed on it by the anterior pituitary and the adrenal cortex. Assuming hexokinase in the normal animal to be continuously moderately inhibited, the action of insulin would be to remove this inhibition and, thus, indirectly to stimulate the enzyme. The phosphorylation of glucose would then proceed more rapidly, glucose would disappear from the extracellular compartment, glucose-6-phosphate would be formed in abundance in muscle and liver cells, and products derived from glucose-6-phosphate would secondarily be formed at greater than normal rates. Essentially all of these effects have been observed to follow the administration of insulin. Insulin lack, on the other hand, would be expected to simulate, chemically, the picture described as following the presence of an excess of hexokinase inhibitor. This picture is, in fact, a good description of the biochemical defect in diabetes mellitus.⁹

The release of insulin by the cells of the islets of Langerhans appears itself to be dependent on the level of blood glucose; the higher the blood glucose, the more insulin discharged. This mechanism is subject to exhaustion, however, and prolonged maintenance of the blood glucose at an excessively high level is followed, in certain species, by irreversible injury to the islets and the picture of permanent diabetes.¹⁰

In the adult normal animal in balance and at constant weight, the glucose made available by the various processes that have been described must be equal to the glucose that is being consumed in the several

processes outlined. The magnitudes of these several processes in human beings have not been exhaustively studied. In the rat it would appear that about one third of the glucose is used in the elaboration of fatty acids which are needed to replenish the fat stores of the body, and only about one thirtieth is required for the maintenance of the glycogen reserves. The remainder is presumed to be degraded ultimately to carbon dioxide and to contribute carbon atoms along the way to other compounds which the body may synthesize from such fragments.

There is no specific nutritional deficiency related to the lack of glucose in the diet. However, it has long been recognized that when, for any reason, the rate of utilization of glucose is subnormal, there is a likelihood of the development of ketonemia and ketonuria. This may arise as a result of deprivation of dietary glucose, diabetes or renal glucosuria and may in general be rectified by the reestablishment, by suitable procedures, of normal glucose catabolism. This action of glucose, its so-called "anti-ketogenic" action, is today fairly well understood. The ketone bodies are not abnormal metabolites, but are formed normally and abundantly in the course of fatty acid degradation, probably chiefly in the liver. They do not accumulate in the blood of the normal person because they are normally consumed in muscle and liver as rapidly as they are formed. Only when they are produced in excessively large amounts do clinical ketonemia and ketonuria develop, and this is undoubtedly what happens when, for one reason or another, glucose is not being utilized at the proper rate. When glucose is scarce, either because of lack of dietary carbohydrate or because of loss of glucose in the urine, or when glucose, though abundantly present, is not being catabolized at a normal rate, excessive quantities of fat are transported from the depots to the liver and there degraded, probably to two-carbon "acetyl" fragments, and a portion of these are converted into acetoacetic acid. If these normal processes

become sufficiently exaggerated, the rate of acetoacetic acid formation will exceed the body's capacity to destroy this compound and its level in the blood will rise. The reestablishment of carbohydrate metabolism in such a subject appears to relieve the liver of the necessity of degrading fatty acids at excessive rates, and as the formation of ketone bodies resumes its normal rate, the ketone bodies which had accumulated in the body are either excreted in the urine or destroyed by the tissues of the body in their normal fashion. It may be noted in passing that acetoacetic acid and "acetyl," with which it is interconvertible, are believed to be catabolized by initial condensation with oxaloacetic acid to yield the same *cis*-aconitic acid encountered in the breakdown of glucose (reaction 24). From this point on the breakdown of acetyl, derived from fatty acids, and of pyruvate, derived from glucose, apparently follow identical pathways.

FUSION OF METABOLIC PROCESSES

From the foregoing discussion it will be apparent that the catabolic pathways of the carbohydrates, fats and proteins cross at many points and that within wide limits one nutrient may be substituted for another without significant injury to the metabolizing tissue. Each of the three major classes of nutrients may supply organic fragments which feed into the tricarboxylic acid cycle, a sequence of reactions which apparently serves to supply a large portion of the energy need of many biologic systems. As this fusion of metabolic pathways has been elucidated, the classic lines of demarcation between the metabolisms of fat, protein and carbohydrate have become progressively more obscure and more meaningless. The picture that is developing is one of reaction sequences, often cyclic, which liberate energy as needed by the organism, and these cycles apparently may be fed at many points and in many ways. Although extreme deviation from the normal composition of the nutrient mixture may result

in the undue accumulation of one or another intermediate, a considerable degree of variation is tolerated. Whereas the catabolic breakdown of protein, fat and carbohydrate will undoubtedly continue to be taught, for purposes of convenience, as separate entities, the better understanding of these processes is leading to a more highly integrated point of view.

Acknowledgments: This paper is one of a series prepared at the request of The Council on Foods and Nutrition of the American Medical Association. With others it will be included subsequently in the Council's "Handbook on Nutrition." This paper appears here through the kindness of Dr. Stetten, Dr. James R. Wilson, Secretary of the Council on Foods and Nutrition, and Dr. Morris Fishbein.

REFERENCES

1. LIPMANN, F. In NORD, F. F. and WERKMAN, C. H. *Advances in Enzymology*. Vol. 1, p. 99. New York, 1941. Interscience Publishers, Inc.
2. BUCHANAN, J. M. and HASTINGS, A. B. The use of isotopically marked carbon in the study of intermediary metabolism. *Physiol. Rev.*, 26: 121, 1946.
3. CORI, C. F. The fate of sugar in the animal body.
 - i. The rate of absorption of hexoses and pentoses from the intestinal tract. *J. Biol. Chem.*, 66: 691, 1925.
- 3a. SWANSON, M. A. The specificity of liver glucose-6-phosphatase. *Federation Proc.*, 8: 258, 1949.
4. CORI, G. T., CORI, C. F. and SCHMIDT, G. Role of glucose-1-phosphate in formation of blood sugar and synthesis of glycogen in liver. *J. Biol. Chem.*, 129: 629, 1939.
5. BARRON, E. S. G. In NORD, F. F. and WERKMAN, C. H. *Advances in Enzymology*. Vol. 3, p. 149. New York 1943. Interscience Publishers, Inc.
- KREBS, H. S. *Advances in Enzymology*, Vol. 3, p. 191. New York, 1943. Interscience Publishers, Inc.
6. SOSKIN, S. and LEVINE, R. *Carbohydrate Metabolism*. Chicago, 1946. University of Chicago Press.
7. STOTZ, E. In NORD, F. F. and WERKMAN, C. H. *Advances in Enzymology*. Vol. 5, p. 129. New York, 1945. Interscience Publishers, Inc.
- OCHOA, S. Muscular contraction: chemical processes of oxidative recovery. *Ann. New York Acad. Sc.*, 47: 835, 1947.
8. CORI, C. F. The Harvey Lectures, 1945-1946. Vol. 41, p. 253. Lancaster, Pa., 1946. Science Press Printing Co.
9. STETTEN, DEW., JR. Endocrine regulation of carbohydrate metabolism. *J. A. M. A.*, 132: 373, 1946.
10. DOHAN, F. C. and LUKENS, F. D. W. Lesions of the pancreatic islets produced in cats by administration of glucose. *Science*, 105: 183, 1947.

Studies in Experimental Diabetes^{*}

R. E. HAIST, M.D.

Toronto, Canada

SINCE Minkowski and von Mering in 1889 first discovered that removal of the pancreas in dogs led to the development of diabetes,¹ much attention has been given to the study of this disease in experimental animals. Depancreatized dogs show the signs and symptoms of diabetes and usually will die in less than three weeks if untreated. They exhibit not only profound changes in the metabolism of carbohydrate but also in the metabolism of protein, as indicated by the increased nitrogen excretion and of fat, as evidenced by excessive ketone body formation; changes abnormal in quantity rather than in kind. The experiments in which the pancreas was removed indicated that normally something was provided by the pancreas which was necessary to prevent the occurrence of diabetes. This was supported by the finding that if a piece of the pancreas was transplanted to another part of the body, diabetes was prevented.² The hormone nature of this pancreatic factor seems obvious now but it was by no means settled until insulin was discovered. It was not until 1922 that a potent, non-toxic extract of pancreas was prepared by Dr. F. G. Banting and Dr. C. H. Best at the University of Toronto.³ By the use of this extract they were able to alleviate the diabetes of depancreatized dogs and later of hospital patients.

The effect of insulin in the diabetic is to relieve the diabetes. However, insulin does not entirely substitute for the removal of the pancreas since the other pancreatic secretions are lacking as well. Depancreatized animals require raw pancreas, lecithin or choline in addition to the insulin or their livers become large and fatty.⁴ Observations

made during the study of experimental diabetes resulted in the discovery of lipotropic factors and the opening of a new field of medical research.

Insulin is produced in the pancreas and there is, as yet, no evidence for any truly extrapancreatic source. It is secreted by the islets of Langerhans, the beta cells of which seem to be the essential endocrine structures. Their importance is indicated by a great deal of evidence not the least of which is the fact that the insulin content of the pancreas under different experimental conditions is closely related to the degree of granulation of the beta cells as shown by the neutral ethyl violet-Biebrich scarlet stain of Bowie.⁵ This stain seems to be superior to most of the special islet stains for demonstrating the changes in granulation of the beta cells although it seems inferior to some in differentiating between the different types of cell in the islet. Using Bowie's stain, when the granulation of the beta cells is reduced, the insulin concentration in the pancreas is diminished also.

It would appear from what has been said that diabetes results from a deficiency of a particular hormone, insulin, manufactured by the beta cells of the pancreatic islets. In fact, we may define diabetes as a chronic metabolic disease which results from a relatively insufficient supply of insulin by the beta cells of the islets of Langerhans. This relative lack may result from a *reduced* insulin *supply* or it may result from a greatly *increased* insulin *need*.

For a while it seemed that the pancreas alone was involved in diabetes but later it appeared that other organs were also implicated. A number of findings led to this

^{*} From the Department of Physiology, University of Toronto, Toronto, Canada.

conclusion. First there was the evidence that in some animal species removal of the pancreas did not lead to the development of a severe diabetes but only to a very mild form of the disease. This suggested that some extra-pancreatic factors must be included in any consideration of the diabetic state. The liver is one organ known to be necessary for the production of diabetes since after removal of the liver the blood sugar falls even in depancreatized animals.⁶ It has been shown, too, that certain endocrine glands other than the pancreas are involved. Houssay and Biasotti in 1930⁷ found that the diabetes resulting from pancreatectomy could be alleviated by removal of the pituitary gland. It was shown by these and other workers that extracts of the anterior pituitary gland would bring back the diabetes once more, and that even in normal intact dogs injections of the extracts gave rise to a diabetic state. Diabetes may be alleviated also by removal of the adrenal glands⁸ and, to a less extent, by removal of the thyroid gland.⁹

As a result of these experiments, it can no longer be said that the absence of beta cells of the islets is responsible entirely for the diabetic picture. It would appear that the presence of the pituitary and certain other endocrine glands is essential, too. There are then two antagonistic systems, one necessary to prevent diabetes and one tending to cause diabetes. When the one tending to cause diabetes predominates, diabetes results.

It will be evident from what has been said that there are many problems remaining in the study of diabetes. These can best be studied in the experimental animal in which conditions may be more or less controlled. Let us look for a moment at the ways in which diabetes can be produced experimentally. It was noted earlier that diabetes can be produced by pancreatectomy. It can be produced, too, by removing almost but not all the pancreas, i.e., by extensive *partial* pancreatectomy. Such a partially depancreatized animal is useful because the changes in the islets of Langerhans in the

remnant of pancreas can be followed. The characteristic changes in the islets found in these diabetic animals are degranulation and hydropic degeneration of the beta cells.^{10,11}

The third method of producing diabetes experimentally is by the injection of extracts of the anterior pituitary gland mentioned briefly before.^{12,13} It should be pointed out that there is a great species difference in the response to these pituitary extracts. Diabetes can be obtained in the intact adult dog or cat by their injection but not in the young of these species nor in the rat, which is very resistant. In the adult dog pituitary diabetes can be separated into two phases, a transient diabetes present during the injections of the extracts and a permanent diabetes which is to be observed, under some circumstances, after the injections of pituitary extracts are stopped.

The diabetes that occurs while the extracts are being injected is known to require the presence of the liver¹⁴ and, according to some, the adrenal glands also.^{8,15} The diabetes resulting from the injection of the extract may be severe, with high fasting blood sugar values, glucosuria, increased ketone body formation and excretion, increased N excretion and other changes characteristic of diabetes. If the extract has not been too potent or the injections too prolonged, the diabetes stops shortly after the injections are discontinued. However, if the effect of the extract is great enough, the diabetes persists after the injections are discontinued, that is, it becomes permanent.

During the course of injections of the anterior pituitary extract certain changes take place in the pancreas. The insulin content of the pancreas is greatly reduced (to less than $\frac{1}{10}$ of the normal value) and there are extensive changes in the islets of Langerhans.^{16,17} The beta cells show progressive degranulation and finally hydropic degenerative changes. If the effect of the injections is not too great, after they are discontinued the islet cells can be restored and the insulin content of the pancreas comes back to normal levels. If the extract

is more potent or the length of administration greater, the islets may be permanently damaged and a permanent reduction in normally functioning beta cells and a permanent lowering of the insulin content of the pancreas result. The persistence of the diabetic state after the anterior pituitary extract is stopped is dependent, therefore, on a permanent reduction in islet tissue; in effect, a removal of the beta cells instead of a removal of the pancreas as a whole. When the anterior pituitary injections are first given, the diabetes is fundamentally a pituitary diabetes (hypophyseal diabetes). Later, the persistence of the diabetic state depends on pancreatic changes and the diabetes is fundamentally pancreatic (metahypophyseal diabetes).

F. G. Young, who first studied metahypophyseal diabetes extensively, has reported recently that in cats a pituitary-induced diabetes may disappear despite the persistence of hydropic degenerative changes in the beta cells of the islets.¹⁸ This observation has not yet been explained. While suppression of endogenous pituitary activity would seem to be the simplest postulated cause, Young states that there is no histologic evidence for this.

It is not possible to discuss here the nature of the diabetogenic pituitary factor. Long and Lukens reported that after removal of the adrenals the diabetogenic effect of pituitary extracts was not observed. This suggests that something acting through the adrenals may be involved. Young believes, however, that the diabetogenic effect of pituitary extracts is not due to an adrenocorticotrophic material (ACTH) since his diabetogenic pituitary preparations produced no obvious response in human patients whereas ACTH has been reported to produce a diabetic state in man. The evidence is increasing that purified growth hormone, as well as adrenocorticotrophic hormone, is diabetogenic in some species.

The importance of the adrenal glands in the genesis of diabetes has been shown by the fact that removal of the adrenals ameliorates to some extent the diabetes

resulting from pancreatectomy. Adrenal cortical substances themselves will cause hyperglycemia and glycosuria when administered in sufficient quantities to normal rats¹⁹ but these changes disappear when the injections cease and no permanent diabetes results. Similar effects have been obtained with pituitary adrenocorticotrophic material (ACTH) in rats,²⁰ and a temporary diabetes resistant to insulin has been induced in man by the administration of purified preparations of ACTH.²¹ A reduced tubular absorption of glucose contributed to the glycosuria in these patients. There was at the same time a decreased concentration of blood glutathione and an increased excretion of uric acid in the urine. These changes are interesting in view of the fact that Griffith²² has reported the production of diabetes in the rabbit by the administration of uric acid in the presence of lowered blood levels of glutathione (see alloxan). The administration of glutathione to subjects showing hyperglycemia and glycosuria as a result of the injections of ACTH caused these changes to be reversed.²³

What has just been discussed constitutes the fourth method by which diabetes may be produced experimentally, namely, by the administration of adrenal cortical substances or by the injection of purified pituitary adrenocorticotrophic materials.

A fifth and lesser diabetogenic effect is that produced by estrogens. Despite the reported fact that estrogens may reduce the amount of insulin which the diabetic patient requires, these materials are diabetogenic in rats whose caloric intake has been maintained by force-feeding. The way in which this effect is brought about is not clear but it is apparently not mediated by the pituitary or adrenal glands.²⁴

Thyroid administration should be included as the sixth way of producing diabetes though this effect has been obtained only when a large part of the pancreas has been removed.²⁵ Thyroid treatment in partially depancreatized diabetic rats, however, caused the diabetic state to disappear.²⁶

The seventh way of producing a permanent diabetes experimentally is by the injection of glucose. Dr. Lukens and Dr. Dohan of Philadelphia showed that repeated intraperitoneal injections of glucose in the cat led to degenerative changes in the islets of Langerhans and to a permanent diabetic state.²⁷

It should be pointed out that the degenerative changes in the islets of Langerhans are much the same in the animals made diabetic by partial pancreatectomy, pituitary injections or glucose injections. In dogs the change is degranulation, hydropic degeneration and finally disappearance of the damaged beta cells, whereas in cats persisting hydropic beta cells are evident. There is good reason to believe that in all these cases the permanent islet changes result from exhaustion of the islet cells through overwork.

The last way of producing diabetes experimentally is by the administration of alloxan, an oxidation product of uric acid.²⁸ The islet changes following alloxan administration differ from those just mentioned. Here there is a specific necrosis of the beta cells, evident in a few hours and followed by the disappearance of beta cells in a few days. These cells apparently disappear without signs of inflammatory reaction. Alpha cells replace beta cells or agranular cells are evident. The insulin content of the pancreas is reduced.²⁹

Doses of alloxan too small to produce diabetes may yet produce some changes in islet function. Subdiabetogenic doses of alloxan have been shown to lead to an impaired tolerance for glucose and to cause an enhanced diabetogenic effect of pituitary extracts in rats.³⁰

Although the type of islet change is different in the alloxan-treated animals (a toxic necrosis rather than hydropic degeneration), the end result is the same, namely, the reduction in functioning beta cells of the islets of Langerhans. With the exception of the alloxan diabetic animals and others in this class, there is good reason to believe that the degenerative islet changes

all result from overfunction of the beta islet cells.

In experimental diabetes the permanence of the state in all instances depends upon some permanent reduction in normally functioning beta cells of the islets of Langerhans. This, coupled with the fact that all types of experimental diabetes can be relieved by insulin, makes it seem possible that diabetes could be cured by sufficiently increasing the amount of insulin-producing tissue in the animal's pancreas. Since this may be so and also since several types of experimental diabetes are produced by exhaustive overwork of the beta cells, it seems important to find out what factors influence the growth of the islets and affect the elaboration and secretion of insulin.

This has been studied by measuring the total volume or weight of the islets and determining the insulin content of the pancreas. It should be pointed out that the insulin content of the pancreas represents a balance between the production of insulin and its liberation or secretion. It may in some instances also bear a relation to the total volume of the insulin-secreting tissue. In itself the insulin content of pancreas may give little information concerning islet function. It may be reduced, for example, by decreased production of insulin or by increased liberation of insulin. However, if the changes in the insulin content of pancreatic tissue are observed under a variety of conditions and other findings are correlated with these, the insulin values become more significant. Two examples will be given:

The first example concerns the effect of partial removal of the pancreas on the insulin content of the pancreatic remnant in the dog.³¹ It is found that if a large but not excessive amount of the pancreas is removed (e.g., $\frac{1}{5}$), the animal does not become diabetic and the insulin content of the pancreas remains within the normal range. Since only one-fifth of the pancreas remains and is supplying sufficient insulin for the animal and yet the insulin concentration in the remnant is not reduced, it

follows that the production and liberation of insulin by the cells of the remnant over a period of time must be increased. The extent of the increase will be related to the amount of pancreas removed. When the amount removed is sufficient to result in diabetes, the insulin concentration in the pancreatic remnant is reduced to low values and the islet cells become hydropic. There seems to be some justification in concluding that the low insulin values and islet cell changes under these circumstances are due to overwork of the islet cells.

The second example concerns the effect of repeated insulin injections upon the insulin content of the pancreas.³² When daily injections of adequate amounts of insulin are given to rats, the insulin content of the pancreas is reduced. Since insulin is being supplied by injection, it seems logical to conclude that the need for endogenous insulin is diminished and that the reduction in insulin content under these circumstances is not due to overactivity of the islets but rather to a *reduced* function of the islet cells. This is supported by the fact that the low insulin values are accompanied by the histologic finding of a lesser number of negative Golgi images in the beta cells of the islets of Langerhans, a finding usually taken to indicate reduced cellular activity. It should be noted, too, that the degree of beta cell granulation is decreased by the injection of insulin.

This brings up the point that a reduction in the specific granulation of the beta cells is related to the insulin concentration in the islet cells rather than to the state of activity of those cells. Hence it is important to recognize that a degranulated beta cell may be one with greatly increased activity or greatly reduced activity.

By comparison of the islet changes with those following partial pancreatectomy and by the use of insulin administration along with other given experimental procedures, it seems possible to conclude whether or not the given procedure itself produces its effect by increasing the activity of the islets or by reducing the activity of the islets. Taken in

relation to other findings and under a variety of experimental conditions it does appear then that studies of the insulin content of pancreas may help to reveal the state of islet function.

The measurement of islet volume or weight is, at best, a tedious procedure but, in the rat, reliable data can be obtained reasonably quickly by the use of a vital staining procedure and a planimetric method of measurement.³³

It is possible to relate some of the findings concerning islet volume and insulin content. It is found first of all that the volume or weight of the islets and the insulin content of the pancreas increase with age or body weight.^{33,34} This seems to hold for humans as well as animals and the relation to body weight according to Ogilvie³⁵ obtains also in the obese human, fatty tissue apparently requiring no less insulin than other tissues. For the rat, within a wide weight range, the insulin concentration per Gm. of pure islet tissue is in the neighborhood of 100 to 200 units. This is the value one might expect in a tumor of pure islet tissue. In one islet tumor a value of 214 units per Gm. has been obtained.³⁶

It has been found that, in general, those factors which reduce insulin production and liberation also reduce the growth of the islets in young rats, and those factors which lead to a stimulation of insulin secretion also increase the growth of the islets in young rats.

We can list the effects on the islets by saying that good examples of factors reducing islet activity and in young rats depressing islet growth are: (1) the repeated injection of insulin, (2) the reduction of the caloric intake and (3) the use of diets low in carbohydrate. Factors stimulating islet secretion and, in young rats, increasing islet growth are: (1) the injection of certain anterior pituitary extracts, (2) the administration of thyroid materials, (3) the use of a high carbohydrate diet and (4) the continuous injection or repeated injections of glucose.

Let us examine these effects briefly. Insulin administration in adequate doses in rats reduces the insulin content of the pancreas to less than half that of the control animals within seven days.³² Such a short period of insulin administration gives no demonstrable reduction in islet volume, hence the change in the insulin content of the pancreas is due to a reduction in the concentration of insulin in the islet cells. When insulin is given to young growing rats for periods of from 20 to 160 days, however, a significant inhibition of the growth of the islets is obtained.³⁷ The total islet weights in the insulin-injected animals were less than in the control rats when compared on the basis of duration of the test or body weight. There is some evidence, too, though not very extensive, that when the insulin injections are discontinued the islet volume is restored to normal in a few weeks. There is as yet no good evidence that insulin administration alone ever reduces the islet tissue below the initial level.

Starvation or undernutrition are other factors exerting an important influence on the islets. Starvation greatly reduces the insulin content of the pancreas.³⁸ Yet starvation of equivalent severity, as judged by the percentage weight loss (17 to 30 per cent), gives no appreciable reduction in the islet volume.³³ Hence the reduction in the insulin content of the pancreas, as with short periods of insulin administration, is due to a reduction in the concentration of insulin in the islet cells. This is borne out by the finding of reduced granulation in the beta cells of the islets in the starved rats. The presence of few negative Golgi images in histologic sections suggests that the effect is related to a reduced activity of the islets, a suggestion that is supported by the finding that the insulin content of the pancreas and beta cell granulation are still further diminished if the fasted animals are injected with insulin.³²

While over short periods, with complete starvation, a reduction in the islet volume was not observed, yet if young animals are undernourished for longer periods of time

an influence on islet growth can be demonstrated.³⁷ When the intake of a balanced diet is just sufficient to maintain body weight but insufficient for growth, it is found after three to five weeks that the islets in the undernourished group have failed to grow, i.e., they do not show the normal increase in islet volume with age. The effects of fasting and undernutrition on islet growth and function are probably due to the restriction of carbohydrate intake. The insulin content of the pancreas is much less after a period on a diet very rich in fat than it is when an equicaloric amount of sugar is given.³⁸

As a result of fasting or undernutrition marked changes in carbohydrate metabolism have been reported, grouped usually under the inclusive term "hunger diabetes." The response to the ingestion of carbohydrate is similar to that of the diabetic. There is hyperglycemia and glycosuria and a high, prolonged glucose tolerance curve. However, these animals differ from the diabetic in that successive doses of carbohydrate improve the condition. It is conceivable that the altered response to carbohydrate by the tissues of the starved animal results from a reduced continuous supply of insulin. Most studies, however, indicate that insulin administration increases the carbohydrate tolerance a little but does not restore it completely. The effect of a continuous injection of insulin should be tested.

Dr. Lundbaek, of Copenhagen, and Dr. Goranson, of Toronto, have shown that in the rat fasting, even for short periods of time, causes a definite increase in the phosphorylase activity of muscle.³⁹ This is due to an increase in the relative proportion of the active *a* form of phosphorylase as compared to the inactive *b* form. The *a* or active form of phosphorylase is thought to be converted to the inactive *b* form through the action of the P-R (prosthetic-group removing) enzyme. Hence an increase in phosphorylase *a* on fasting suggests that the action of this P-R enzyme has been diminished. The change in phosphorylase activity and presumably of the P-R enzyme is quickly reversed by refeeding the fasted animal. An

increase in phosphorylase activity on fasting probably assists in the mobilization of glycogen stores at a time when no exogenous carbohydrate is available.

It seems obvious that the effect of fasting on carbohydrate metabolism must be due to some alteration in the activity of those tissues which are important in the new production, storage, liberation or use of sugar. One of the important changes may be the increase in phosphorylase activity which has just been discussed.

Diet also affects the volume of the islets of Langerhans. It has been shown by Tjening that growing animals on a high fat diet for a long period of time have a smaller volume of islet tissue than those fed a high carbohydrate diet.⁴⁰ The various factors mentioned, insulin administration, fasting or undernutrition and high fat or low carbohydrate intake, appear to decrease the insulin content of pancreas and to diminish the growth of the islets in young rats as a compensation for a diminished need for endogenous insulin.

The factors stimulating islet activity are those which increase the need for insulin. Young and his associates showed that injections of crude saline extracts of the anterior pituitary gland lead to an increase in insulin content of pancreas⁴¹ and to increased islet growth in young rats.⁴² We have confirmed the effect on islet growth.³⁷ A positive correlation between islet size and the size of the pituitary has been reported by Tjening. While these facts point to a pituitary pancreatic effect, the evidence that the pituitary gland normally exerts any essential regulation of islet function is not at all convincing. Krischesky⁴³ reports an increase in islet tissue following hypophysectomy in the rat, although his published data could be interpreted as showing no significant change. In our studies it was found that hypophysectomy does not lead to any significant reduction in the insulin content of the pancreas or the islet volume below that of paired-fed control animals although the values obtained are considerably less than in control animals fed *ad libitum*.³⁷ Any

effects that do occur in the hypophysectomized animals might be ascribed to undernutrition. Moreover, the insulin-lowering effect of fat-feeding can still be obtained after removal of the pituitary gland and, having been lowered, the insulin content can be restored again to normal in such an animal by feeding a balanced diet.⁴⁴ These findings would seem to indicate that the pituitary is not fundamentally involved in these changes. The pancreas seems able to regulate the production and liberation of insulin independently of the pituitary gland.

Administration of desiccated thyroid also is reported to lead to an increase in the insulin content of pancreas⁴⁵ and it has been found that there is also an increase in the total bulk of the islets.³⁷ The effect on islet volume could not be demonstrated satisfactorily until after forty days. This is interesting in view of the report by Houssay and associates that the diabetes of partially depancreatized rats disappears as a result of thyroid treatment.²⁶

By far the most rapid effect on the growth of the islets, with the factors yet investigated, is obtained by the continuous injection of glucose. This had been reported by Woerner to cause an increase in islet volume in guinea pigs⁴⁶ but quantitative data were not available. It was found in the experiments at the University of Toronto that the continuous injection of glucose intravenously for seven to ten days caused a marked increase in the mass of islet tissue in growing rats.³⁷ In fact, the islet tissue was doubled in volume in this time. From this it would appear that in a normal, intact, growing rat the islet tissue is very labile and responds to stimulation by growth as well as secretion. Work done in order to find whether or not the effect is mediated by the pituitary gland has been inconclusive as yet.

There is evidence that the activity of islet cells is stimulated by conditions elevating the blood sugar level. Whether or not the elevated blood sugar acts as a direct stimulus for the islets or whether blood insulin level is involved cannot be decided

at present. The experiments of Anderson⁴⁷ on the isolated perfused pancreas support the view that blood sugar level is the important factor. The recent experiments reported by Milman and Russell⁴⁸ are interesting in this regard. They found that highly purified growth hormone when injected intraperitoneally into normal male rats caused a significant and prolonged reduction in blood sugar level. In alloxanized or partially depancreatized rats, however, the injection of this material caused a rise in the blood sugar values. It is possible that the differences in the effects might be due to changes in the response of tissues in the presence of adequate or small amounts of insulin. It would seem more probable, however, that the pituitary growth hormone produces hyperglycemic or contra-insulin effects, but in the presence of adequate islet tissue these lead to a sufficient secretion of insulin to cause hypoglycemia. Since the effect is very prolonged, it would suggest either that insulin secretion may be stimulated in the presence of a falling blood sugar level or that the insulin secreted by the pancreas has a very prolonged effect. The experiments lend support to the view that some factor other than blood sugar level, possibly blood insulin level, is important in the stimulation of the secretion of insulin by the islet cells. Another interesting experiment not supporting this view is that of Peterson⁴⁹ who injected glucose quickly into the heart in large doses and found that in fifteen minutes there was degranulation of the beta cells of the islets. This degranulation was not prevented by the injection of insulin along with the glucose.

Because a procedure leads to an increase in the islet tissue in the rat does not mean that such a procedure is good or bad as far as the prevention of diabetes is concerned. Growth, in these experiments, can be considered as an evidence of islet stimulation.

It will be apparent that the factors which we have cited as increasing the insulin content or islet volume in the rat, namely, the administration of pituitary extract, thyroid extract or large amounts of sugar, are all

diabetogenic in the adult dog or cat, i.e., they help to produce diabetes in these animals. In the intact rat, diabetes probably does not occur either because the increase in functioning islet tissue is great enough or because these factors do not increase the need for insulin as greatly in the rat as in the dog. At all events the compensatory increase in the insulin producing structures and in insulin secretion is great enough to prevent the onset of diabetes.

We can conclude from these data that certain factors stimulate the islets and certain factors depress them. In experimental animals the stimulating factors may produce diabetes; but if there is a sufficient compensatory increase in islet tissue and insulin secretion, diabetes may not occur. There is a species difference in this response and it is important to discover the reason for this difference.

One further point should be mentioned and that is that those factors which reduce islet activity can prevent or at least reduce the damaging effects on the islets of other procedures which ordinarily stimulate the islets excessively.⁵⁰ Fasting, fat-feeding or insulin administration, for example, all tend to prevent the injurious effects of pituitary injections on the islets of dogs, and fasting or insulin administration prevents the islet changes in animals with extensive partial pancreatectomy. The observation of Housay and Martinez⁵¹ of an adverse effect of fat in 95 per cent depancreatized rats is difficult to reconcile with these findings and further clarification of the effect of fat is required.

We know then that there are certain factors which stimulate the islets and which when excessive, or under certain other conditions, may cause diabetes. It is apparent, too, that certain other factors depress islet activity and can prevent the excessive stimulation of the islet cells, hence can prevent most but not all forms of diabetes in experimental animals. The exception is the diabetes resulting from the administration of alloxan.

Much remains to be done in elucidating the cause of diabetes and in finding factors which influence islet growth. Perhaps human diabetes can be prevented or cured. Much experimental work must be done in the investigation of the complications of diabetes, especially the vascular, renal and ocular changes. Investigations in this field are just beginning. Another problem requiring clarification is the effect of removal of the pancreas in alloxan diabetes, pituitary diabetes and human diabetes. Some report a decrease in insulin requirements^{52,53} and others no change.⁵⁴ When a decrease is found, this may conceivably be due to an altered absorption of food materials or possibly to the removal of some influence of a pancreatic hyperglycemic factor. Hence the physiologic significance of the hyperglycemic factor must be determined.

We have mentioned the ways in which diabetes can be produced experimentally and have intimated that in all instances the existence of diabetes could be ascribed to a relative lack of insulin. Yet we have given no indication of how insulin acts or what essential changes are occurring in the tissues of the diabetic. We cannot at this point enter into a discussion of the mode of action of insulin. Its essential action is probably on some of the enzyme systems involved in the intermediate metabolism of carbohydrate. Cori and associates reported that insulin exerts an influence on the hexokinase system which is responsible for the phosphorylation of glucose and the bringing of it into the metabolic chain in the tissue cells.⁵⁵ Others have postulated different sites of action for insulin. Recently support has been found for a more generalized influence, namely, an increase in the efficiency of the coupling between phosphorylation and oxidation.

Goranson⁵⁶ has observed that the aerobic phosphorylation of creatine during succinate or malate oxidation in heart muscle preparations from alloxan diabetic rats was significantly less than in the normal although no significant difference in oxygen uptake was noted. Insulin injected into the

alloxanized rats prior to the test caused no appreciable change in the oxygen consumption of heart muscle preparations but restored the ability of the tissue to synthesize phosphocreatine. This and other evidence led him to the conclusion that insulin participates directly in reactions in the tricarboxylic acid cycle leading to a more efficient coupling between the processes of phosphorylation and oxidation. According to present concepts the synthesis of adenosine triphosphate and phosphocreatine represent the chief means whereby the potential energy of carbohydrate, and presumably of the breakdown products of fat and protein, too, is transferred to energy-utilizing systems. Hence the more efficient coupling between the processes of phosphorylation and oxidation brought about by insulin would lead to an increase in the efficiency with which the potential energy of carbohydrate is made available for such endergonic processes as the synthesis of glycogen and other cellular components. Data are accumulating concerning the mode of action of insulin and one can assume that before long some fundamental action will be established.

We are not satisfied, however, with the state of our knowledge concerning experimental diabetes. Let me end by quoting Oscar Minkowski,⁵⁷ the man who first depancreatized a dog, produced and recognized experimental diabetes. "It may be useful . . . to point out, which the discovery of insulin shows clearly, that scientific research which does not lead immediately to a practical end, sooner or later may have success in practice. Also it is not necessary to solve every problem regarding the elements of nature in order to serve mankind. It is sufficient to search for the laws by which they work in order to master them."

REFERENCES

1. VON MERING, J. and MINKOWSKI, O. Diabetes Mellitus nach Pankreasextirpation. *Arch. f. exper. Path. u. Pharmacol.*, 26: 371, 1889.
2. HÉDON, E. Greffe sous-cutanée du pancréas. *Compt. rend. Soc. de biol.*, 44: 307, 1892. Ibid. Greffe sous-cutanée du pancréas; ses résultats au point de vue

- de la théorie du diabète pancréatique. 44: 678, 1892. MINKOWSKI, O. Untersuchungen über Diabetes Mellitus nach Exstirpation des Pankreas. *Arch. f. exper. Path. u. Pharmacol.*, 31: 85, 1893.
3. BANTING, F. G. and BEST, C. H. The internal secretion of the pancreas. *Am. J. Physiol.*, 59: 479, 1922; *J. Lab. & Clin. Med.*, 7: 251, 1921-1922.
 4. HERSHEY, J. M. and SOSKIN, S. Substitution of "lecithin" for raw pancreas in the diet of the depancreatized dog. *Am. J. Physiol.*, 98: 74, 1931. BEST, C. H., HERSHEY, J. M. and HUNTSMAN, M. E. The effect of lecithine on fat deposition in the liver of the normal rat. *J. Physiol.*, 75: 56, 1932.
 5. BEST, C. H., CAMPBELL, J., HAIST, R. E. and HAM, A. W. The effect of insulin and anterior pituitary extract on the insulin content of the pancreas and the histology of the islets. *J. Physiol.*, 101: 17, 1942.
 6. MANN, F. C. and MAGATH, T. B. The effect of total removal of the liver after pancreatectomy on the blood sugar level. *Arch. Int. Med.*, 31: 797, 1923.
 7. HOUSSAY, B. A. and BIASOTTI, A. Hypophysectomie et diabète pancréatique chez le crapaud. *Compt. rend. Soc. de biol.*, 104: 407, 1930. Ibid. Le diabète pancréatique des chiens hypophysectomisés. *Compt. rend. Soc. de biol.*, 105: 121, 1930.
 8. LONG, C. N. H. and LUKENS, F. D. W. The effects of adrenalectomy and hypophysectomy upon experimental diabetes in the cat. *J. Exper. Med.*, 63: 465, 1936.
 9. DOHAN, F. C. and LUKENS, F. D. W. The effect of thyroidectomy upon pancreatic diabetes in the cat. *Am. J. Physiol.*, 122: 367, 1938. WILDER, R. M., FOSTER, R. F. and PEMBERTON, J. DE J. Total thyroidectomy in diabetes mellitus. *Endocrinology*, 18: 455, 1934.
 10. HOMANS, J. The relation of the islets of Langerhans to the pancreatic acini under various conditions of secretory activity. *Proc. Roy. Soc. B.*, 86: 73, 1913. HOMANS, J. Degeneration of the islands of Langerhans associated with experimental diabetes in the cat. *J. M. Research*, 30: 49, 1914.
 11. ALLEN, F. M. Studies Concerning Glycosuria and Diabetes. Boston, 1913. Harvard University Press. ALLEN, F. M. Hydropic degeneration of islands of Langerhans after partial pancreatectomy. *J. Metab. Research*, 1: 5, 1922.
 12. HOUSSAY, B. A., BIASOTTI, A. and RIETTI, C. T. Diabetogenic action of anterior lobe extracts. *Compt. rend. Soc. de Biol.*, 111: 479, 1932.
 13. YOUNG, F. G. Permanent experimental diabetes produced by pituitary (anterior lobe) injections. *Lancet*, 2: 372, 1937.
 14. HOUSSAY, B. A. Diabetes as a disturbance of endocrine regulation. *Am. J. M. Sc.*, 193: 581, 1937.
 15. LONG, C. N. H., KATZIN, B. and FRY, E. G. The adrenal cortex and carbohydrate metabolism. *Endocrinology*, 26: 309, 1940.
 16. BEST, C. H., CAMPBELL, J. and HAIST, R. E. The effect of anterior pituitary extract on the insulin content of the pancreas. *J. Physiol.*, 97: 200, 1939.
 17. HAM, A. W. and HAIST, R. E. Histological study of trophic effects of diabetogenic anterior pituitary extracts and their relation to the pathogenesis of diabetes. *Am. J. Path.*, 17: 787, 1941.
 18. YOUNG, F. G. Metabolism in experimental diabetes mellitus. *Lancet*, 2: 955, 1948.
 19. INGLE, D. J., SHEPPARD, R., OBERLE, E. A. and KUIZENGA, M. H. Comparison of acute effects of corticosterone and 17-hydroxycorticosterone on body weight and urinary excretion of sodium, chloride, potassium, nitrogen and glucose in normal rat. *Endocrinology*, 39: 52, 1946.
 20. INGLE, D. J., LI, C. H. and EVANS, H. M. Effect of adrenocorticotrophic hormone on urinary excretion of sodium, chloride, potassium, nitrogen and glucose in normal rats. *Endocrinology*, 39: 32, 1946.
 21. CONN, J. W., LOUIS, L. H. and JOHNSTON, M. W. Studies upon mechanisms involved in the induction with adrenocorticotrophic hormone of temporary diabetes mellitus in man. *Proc. Am. Diabetes A.*, 8: 215, 1948.
 22. GRIFFITHS, M. Uric acid diabetes. *J. Biol. Chem.*, 172: 853, 1948.
 23. CONN, J. W., LOUIS, L. H. and JOHNSTON, M. W. Alleviation of experimental diabetes in man by administration of reduced glutathione (GSH): metabolic implications. *Science*, 109: 279, 1949.
 24. INGLE, D. J. The relationship of the diabetogenic effect of diethylstilbestrol to the adrenal cortex in the rat. *Am. J. Physiol.*, 138: 577, 1943. INGLE, D. J. The diabetogenic effect of diethylstilbestrol in adrenalectomized-hypophysectomized partially depancreatized rats. *Endocrinology*, 34: 361, 1944.
 25. HOUSSAY, B. A. Thyroid and metathyroid diabetes. *Endocrinology*, 35: 158, 1944.
 26. HOUSSAY, B. A., FOGLIA, V. G. and MARTINEZ, C. Influence of thyroid on alloxan and pancreatic diabetes in rat. *Endocrinology*, 39: 361, 1946.
 27. DOHAN, F. C. and LUKENS, F. D. W. Lesions of the pancreatic islets produced in cats by administration of glucose. *Science*, 105: 183, 1947. Experimental diabetes produced by the administration of glucose. *Endocrinology*, 42: 244, 1948.
 28. DUNN, J. S., SHEEHAN, H. L. and McLEITCHIE, N. G. B. Necrosis of islets of Langerhans produced experimentally. *Lancet*, 1: 484, 1943. DUNN, J. S., KIRKPATRICK, J., McLEITCHIE, N. G. B. and TELFER, S. V. Necrosis of the islets of Langerhans produced experimentally. *J. Path. & Bact.*, 55: 245, 1943.
 29. RIDOUT, J. H., HAM, A. W. and WRENSHALL, G. A. The correlation of the insulin content and the histological picture of the pancreas at intervals after the administration of alloxan. *Science*, 100: 57, 1944.
 30. SHIPLEY, E. G. and RANNEFELD, A. N. Glucose tolerance in rats following repeated small doses of alloxan. *Endocrinology*, 37: 313, 1945.
 31. BELL, H. J., BEST, C. H. and HAIST, R. E. The effect of partial pancreatectomy on the concentration of insulin in the pancreatic remnant. *J. Physiol.*, 101: 11, 1942.
 32. BEST, C. H. and HAIST, R. E. The effect of insulin administration on the insulin content of the pancreas. *J. Physiol.*, 100: 142, 1941.
 33. HAIST, R. E. and PUGH, E. J. Volume measurement of the islets of Langerhans and the effects of age and fasting. *Am. J. Physiol.*, 152: 36, 1948.
 34. HAIST, R. E. and BELL, H. J. Adrenalectomy, gonadectomy and the insulin content of the pancreas. *Am. J. Physiol.*, 141: 606, 1944.

35. OGILVIE, R. F. A quantitative estimation of the pancreatic islet tissue. *Quart. J. Med.*, 6: 287, 1937.
36. HAIST, R. E. Factors affecting the insulin content of the pancreas. *Physiol. Rev.*, 24: 409, 1944.
37. HAIST, R. E., EVANS, M. J., KINASH, B., BRYANS, F. E. and ASHWORTH, M. A. Factors affecting the volume of the islands of Langerhans. *Proc. Am. Diabetes A.*, 9: 1949.
38. BEST, C. H., HAIST, R. E. and RIDOUT, J. H. Diet and the insulin content of pancreas. *J. Physiol.*, 97: 107, 1939.
39. LUNDBÄCK, K. and GORANSON, E. S. Increased muscle phosphorylase activity in the rat. *Nature*, 162: 1002, 1948.
LUNDBÄCK, K. and GORANSON, E. S. The effect of fasting on muscle phosphorylase activity in the rat. *Acta med. Scandinav.*, 17: 280, 1949.
40. TEJNING, S. Dietary factors and quantitative morphology of the islets of Langerhans. *Acta med. Scandinav.*, Supp. 198: 1, 1947.
41. MARKS, H. P. and YOUNG, F. G. The hypophysis and pancreatic insulin. *Lancet*, 1: 493, 1940.
42. RICHARDSON, K. C. and YOUNG, F. G. The "pancreatotropic" action of anterior pituitary extracts. *J. Physiol.*, 91: 352, 1937.
43. KRICHESKY, B. Relation of anterior pituitary to the volume of islet tissue in the male rat. *Proc. Soc. Exper. Biol. & Med.*, 34: 126, 1936.
44. HAIST, R. E. The pituitary and the insulin content of pancreas. *J. Physiol.*, 98: 419, 1940.
45. FRAENKEL-CONRAT, H., HERRING, V. V., SIMPSON, M. E. and EVANS, H. M. Effect of thyroxin on the insulin content of the rat's pancreas. *Endocrinology*, 30: 485, 1942.
46. WOERNER, C. A. Studies of the islands of Langerhans after continuous injections of dextrose. *Anat. Rec.*, 71: 33, 1938.
47. ANDERSON, E. and LONG, J. Effect of hyperglycemia on insulin secretion as determined with the isolated rat pancreas in a perfusion apparatus. *Endocrinology*, 40: 92, 1947.
48. MILMAN, A. E. and RUSSELL, J. A. Effects of growth hormone on the blood sugar and insulin sensitivity of the rat. *Federation Proc.*, 8: 111, 1949.
49. PETERSON, C. A. Degranulation of beta cells of rat's pancreas by glucose correlated with alterations in glucose tolerance. *Proc. Soc. Exper. Biol. & Med.*, 70: 352, 1949.
50. HAIST, R. E., CAMPBELL, J. and BEST, C. H. The prevention of diabetes. *New England J. Med.*, 607: 223, 1940.
51. HOUSSAY, B. A. and MARTINEZ, C. Experimental diabetes and diet. *Science*, 105: 548, 1947.
52. THOROGOOD, E. and ZIMMERMAN, B. Effects of pancreatectomy on glycosuria and ketosis in dogs made diabetic by alloxan. *Endocrinology*, 37: 191, 1945.
53. BRUNSCHWIG, A., RICKETTS, H. T. and BIGELOW, R. R. Total pancreatectomy, total gastrectomy, total duodenectomy, splenectomy, left adrenalectomy and omentectomy in a diabetic patient, recovery. *Surg., Gynec. & Obst.*, 80: 252, 1945.
54. CAMPBELL, J., KEENAN, H. C. and BEST, C. H. Further observations on dogs made permanently diabetic by the administration of extracts of the anterior pituitary gland. *Am. J. Physiol.* 126: 455, 1939.
55. COLOWICK, S. P., CORI, G. T., SLEIN, M. W. The effect of adrenal cortex and anterior pituitary extracts and insulin on the hexokinase reaction. *J. Biol. Chem.*, 168: 583, 1947. CORI, C. F. Enzymatic reactions in carbohydrate metabolism. *Harvey Lect.*, 41: 253, 1945.
56. GORANSON, E. S. Reduced synthesis of phosphocreatine in tissue homogenates from alloxan diabetic rats. *Federation Proc.*, 8: 58, 1949.
57. MINKOWSKI, O. Historical review of diabetes. *München. med. Wchnschr.*, 76: 311, 1929.

Association of Diabetes Mellitus and Disorders of the Anterior Pituitary, Thyroid and Adrenal Cortex*

WILLIAM M. BALFOUR, M.D. and RANDALL G. SPRAGUE, M.D.

Rochester, Minnesota

IN most instances the disturbed metabolism of human diabetes mellitus is explainable on the basis of deficiency of insulin. In remarkably few cases, either preceding or following establishment of the diabetic state, is there clear evidence of disturbance of function of other glands of internal secretion which are known to play an important role in carbohydrate metabolism. In the majority of cases of diabetes the function of the anterior pituitary, thyroid and adrenal cortex is normal by all clinically available methods of measurement.

Nevertheless, there is good evidence that hyperfunction of the anterior pituitary, thyroid or adrenal cortex may, in an occasional case, contribute to the development of diabetes in susceptible individuals, or may intensify diabetes which is already existing. By the same token, when hypofunction of these glands of internal secretion results from destructive lesions or surgical extirpation, existing diabetes may be ameliorated in varying degrees.

In some cases of tumors of the pituitary or adrenal cortex, or of hyperplasia of the adrenal cortex, diabetes occurs and is apparently due primarily to hyperfunction of the involved gland. In such instances the presence of other stigmas of hyperfunction of the gland in question usually serve to distinguish the associated diabetes from the commonly observed forms of the disease. Furthermore, in such cases all evidences of diabetes may disappear when and if normal

function of the anterior pituitary or adrenal cortex is restored.

Evidences of diabetes may also be observed in cases of thyrotoxicosis and may disappear with the restoration of normal function of the thyroid. Many authors regard these as cases of latent diabetes which are brought to light by the metabolic stress of hyperthyroidism rather than as cases of diabetes resulting solely from hyperthyroidism.

Animal experimentation has gone far in elucidating the role of the anterior pituitary, thyroid and adrenal cortex in carbohydrate metabolism, particularly the disturbed carbohydrate metabolism of experimental diabetes. What has been learned in this field from the study of animals can occasionally be applied directly to the human being. It is our purpose to present a group of cases of diabetes mellitus from the records of the Mayo Clinic in which the development or behavior of the disease was modified by either hypofunction or hyperfunction of the anterior pituitary, thyroid or adrenal cortex, and to discuss briefly the physiologic principles involved.

ANTERIOR PITUITARY AND HUMAN DIABETES

Diabetes Mellitus Associated with Acromegaly and with Hypopituitarism. That the anterior lobe of the pituitary body has profound effects on carbohydrate metabolism has been shown in many ways experimentally. Diabetes in depancreatized animals is

* From the Division of Medicine, Mayo Clinic, Rochester, Minn.

made milder by hypophysectomy, as was demonstrated by Houssay¹ in his classic experiments. The diabetes of the Houssay animal is intensified by the administration of extracts of the anterior pituitary. Furthermore, as shown by Young,² permanent diabetes can be induced in animals by the administration of extracts of the anterior lobe of the pituitary. These facts and other evidence would suggest that hyperfunctioning lesions of the anterior lobe of the pituitary in human beings might frequently be associated with diabetes. This is at least partially true in that a higher incidence of diabetes occurs among patients with acromegaly than would be expected by chance. However, all patients with comparable hyperfunctioning lesions of the anterior pituitary are not diabetic and it is possible that a fundamental deficiency of the islets of Langerhans must exist before a hyperactive lesion of the pituitary can produce diabetes. The diabetes in these cases usually is mild and relatively insensitive to insulin. When the lesion of the pituitary becomes inactive, either spontaneously or as a result of treatment, the diabetes may become milder or may, for all practical purposes, disappear. The following case illustrates some of these points.

CASE 1. A white woman, fifty-five years of age, was well until October, 1948, when she noted the gradual onset of fatigue, pruritus vulvae, polydipsia, polyuria, loss of weight and blurring of vision. Glycosuria and a concentration of blood sugar of 384 mg. per 100 cc. were discovered by her physician and a diabetic diet was prescribed. Insulin was not used. The diabetes on her admission to the clinic a few weeks later was uncontrolled.

The appearance of the patient at this time suggested acromegaly. Her hands and feet were large and she stated that the size of her glove had increased from 6½ to 9 and that her shoes had to be wider but no longer than formerly. These changes had developed gradually during the previous two years. On questioning she admitted that headaches in the frontal region were rather frequently present in the mornings on arising. Prognathism was not present. Roent-

genograms of the skull showed evidence of an enlarged sella turcica owing to an intrasellar tumor with decompression into the sphenoid sinus. A roentgenogram of a hand showed evidence considered typical of acromegaly. The value for blood sugar was 370 mg. per 100 cc. Urinary excretion of 17-ketosteroids was 11.7 mg. in twenty-four hours. The concentration of phosphate in the plasma was 3.3 mg. per 100 cc. The basal metabolic rate was +20 per cent. Visual fields were normal as were the ocular fundi. Results of neurologic examination were negative.

Diagnoses of pituitary tumor with acromegaly and diabetes mellitus were made. The diabetes was brought under control with some difficulty, but in about five days the sugar in the urine was markedly reduced. A mixture of insulin containing 20 units of protamine zinc and 42 units of regular insulin was given each morning before breakfast. The diet consisted of 1,962 calories. Insulin reactions did not occur. A course of roentgen therapy was given for the tumor of the pituitary and the patient was permitted to return home and advised to continue use of the aforementioned dose of insulin and diet.

When the patient returned in five weeks for a second course of roentgen therapy, she told of a striking change in the diabetes. During the first two weeks at home she continued to need a total of 62 units of insulin daily. An increased amount of sugar appeared in the urine during an upper respiratory infection. After this, however, there was a rapid drop in the requirement for insulin. During the second visit it was found that 10 units of protamine zinc insulin daily kept her urine free of sugar. On fasting the concentration of blood sugar was 147 mg. per 100 cc. Her strength had increased and she felt well. The second course of roentgen therapy was given.

Again, after an interval of five weeks, the patient returned for a third course of roentgen therapy. At this time the dosage of insulin was 6 units of protamine zinc daily. The urine was consistently free of sugar.

She did well for the next two weeks and then symptoms of increased intracranial pressure developed rather rapidly with headaches, vomiting and finally unconsciousness. She was brought to the clinic and immediately hospitalized; a lumbar puncture was cautiously performed. This revealed a protein content of 110 mg. per 100 cc. and 18 lymphocytes and 21 polymorphonuclear cells per cubic milliliter. The most

probable diagnosis was meningeal irritation associated with rupture of the intrasellar tumor. Treatment was conservative and recovery occurred slowly. During the period of increased stress the fasting blood sugar varied from 130 to 168 mg. per 100 cc. Insulin was not required and there was no glycosuria. At the time of her dismissal she was not taking any insulin and was again feeling well. Visual fields still showed no encroachment. The basal metabolic rate was +16 per cent.

This patient had apparently had active acromegaly due to a tumor of the pituitary for about two years at the time diabetes developed. The diabetes was not mild but was rather insulin-insensitive. Roentgen ray treatment of the pituitary gland was followed in several weeks by a rapid decrease in the severity of the diabetes. It cannot be concluded with certainty that the amelioration of the diabetic state was due solely to a decrease in function of the pituitary as the same type of change in severity of diabetes is occasionally seen when the disease is first brought under control. However, the fact that treatment for acromegaly was followed by such a profound change in the diabetes is highly suggestive. That the diabetes was actually milder after the treatment of the pituitary is further indicated by the fact that the stress of the severe illness described did not produce, temporarily, a more severe diabetic condition than was present before.

Almy and Shorr³ have recently described a case of diabetes mellitus made manifest by acromegaly which disappeared completely when hypofunction of the anterior pituitary appeared. An abstract of the case is given here because evidence for hypofunction of the pituitary is stronger than it is in our case.

A man, forty years of age, had had acromegaly for fourteen years and diabetes for five years. The diabetes was relatively insensitive to insulin in that 60 units of protamine zinc insulin did not reduce the amount of sugar in the urine. The glucose tolerance curve indicated the presence of diabetes. Acute mastoiditis and basilar meningitis developed and mastoidectomy was performed. Eighteen days later the urine

was free of sugar and fasting blood sugar and glucose tolerance curves became normal. Five years later he was still free of diabetes. During this period the sella turcica became reduced in size and the basal metabolic rate dropped to -30 per cent. There was no evidence of adrenal insufficiency. The authors attributed the sudden disappearance of the diabetes to partial degeneration of the anterior pituitary with consequent reduction in the elaboration of the diabetogenic principle.

Neither of these cases describes the appearance of hypofunction of the anterior pituitary of a patient with true diabetes mellitus, that is, diabetes due solely to a deficiency of insulin. Such an occurrence must be exceedingly rare. A search of the records of the Mayo Clinic for the past fifteen years reveals no authenticated case. Theoretically such a patient should show amelioration of the diabetes, just as pancreatic diabetes in the experimental animal is ameliorated by hypophysectomy.

THYROID GLAND AND HUMAN DIABETES

Diabetes Mellitus and Hyperthyroidism. An excess of thyroid hormone in non-diabetic individuals may produce glucose tolerance curves resembling those of patients with mild diabetes mellitus. This is probably due in part to an increased rate of absorption of glucose from the gastrointestinal tract and perhaps in part to impairment of the capacity of the liver to store glucose as glycogen. When hyperthyroidism develops in a case of diabetes, the decreased sugar tolerance already existing is further depressed and the diabetes becomes more severe. It is also important to note that diabetes may first become manifest with the onset of hyperthyroidism. All symptoms may easily be attributed to the uncontrolled diabetes and the diagnosis of hyperthyroidism overlooked. Any new diabetic who continues to lose weight and complains of excessive fatigue and nervousness after control of the diabetes has been accomplished should be suspected of having hyperthyroidism. This is especially true if the diabetes proves to be unexpectedly

difficult to control. Some of these points are illustrated in the following case reports.

CASE II. A white male, thirty-four years of age, was first seen at the clinic in April, 1934. He gave a history of diabetes mellitus of seven

Partial control of the glycosuria was obtained the day after operation with 90 units of insulin. The next three days after operation his insulin requirement gradually rose so that on the fourth postoperative day he was given 150 units. After this there was a gradual decrease in the amount

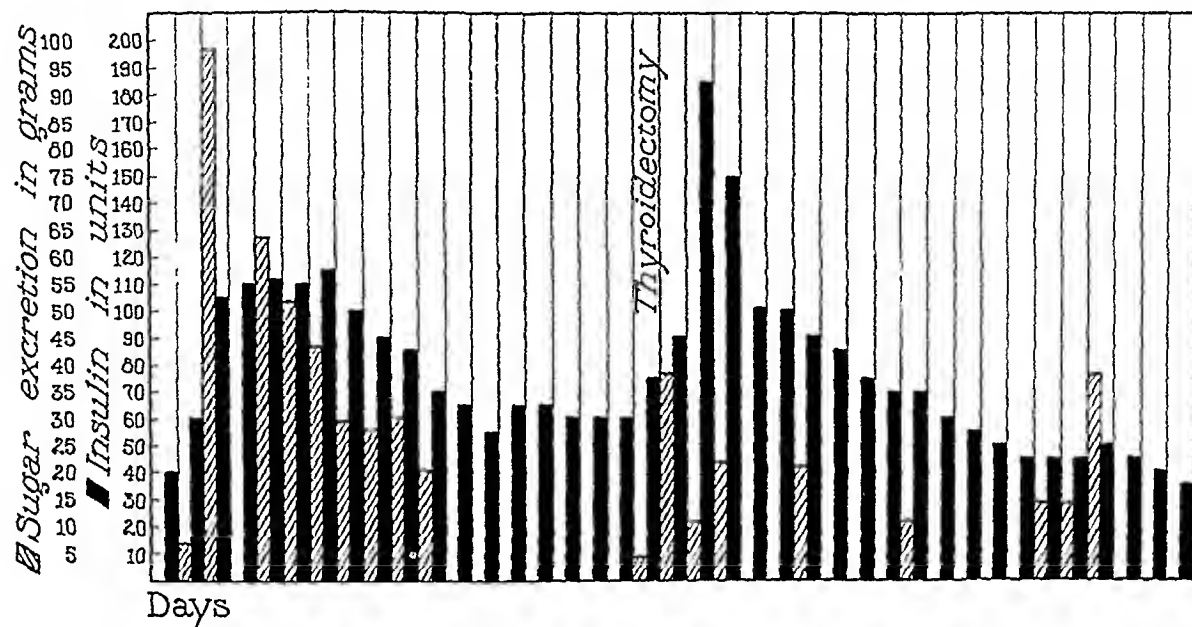


FIG. 1. The effect of thyroidectomy on excretion of glucose and requirement of insulin. (Case. II.)

years' duration. Control had been good on three doses of regular insulin daily averaging 20 units each, for most of the seven years. However, increasing difficulty had been experienced in his diabetic management during the two years prior to his admission to the clinic. During this period he had noted weakness, increased perspiration, nervousness and intermittent watery diarrhea. There were many periods of heavy glycosuria and many severe insulin reactions. He was hospitalized on admission to the clinic in an attempt to control the diabetes. He required up to 115 units of regular insulin daily in divided doses. Even with this amount of insulin he excreted large amounts of glucose. (Fig. 1.) On a diet containing 113 Gm. of carbohydrate he excreted 98 Gm. of glucose in one period of twenty-four hours and 63 Gm. in another. Reactions were still frequent. A diagnosis of exophthalmic goiter was made on the basis of the signs and symptoms. The basal metabolic rate was +18 per cent. He was given strong iodine solution (Lugol's solution), 10 drops three times a day. With partial control of the hyperthyroidism by the iodine, his requirement of insulin dropped to 60 units daily. A subtotal thyroidectomy was performed and 28 Gm. of tissue were removed. The pathologic diagnosis was parenchymatous hypertrophy.

of insulin required to control the diabetes. Three weeks after operation the urine was free of sugar on 35 units of insulin in three doses daily. This was the smallest dose of insulin he had ever taken.

CASE III. A white woman, forty-eight years of age, was first seen at the clinic in 1930. At this time a diagnosis of diabetes mellitus was made. Glycosuria was controlled on three doses of regular insulin a day. The total daily dosage was 40 units. During the next two years under her physician's care she was able to discontinue the use of insulin. She remained well until two months before her second admission to the clinic in 1933 at which time she began to experience weakness, palpitation, excessive perspiration, edema of the ankles and some loss of weight in spite of an excellent appetite. Shortly before her return to the clinic her blood sugar was found to be 300 mg. per 100 cc. Insulin was again employed and at the time of her admission she was taking 45 units daily in three doses. Nevertheless, she was still excreting moderate amounts of glucose in the urine. A diagnosis of exophthalmic goiter was made. The basal metabolic rate was +26 per cent. Administration of strong iodine solution, 10 drops three times a day, was started. Partial control of the hyperthyroidism was obtained but the insulin require-

ment increased until the day before operation, when 70 units were required. (Fig. 2.) After operation there was increased difficulty in controlling the diabetes. On the ninth post-operative day 155 units of insulin were given with only fair control of the glycosuria. The

CASE IV. This case has previously been discussed by McDonough, Haines and Kepler.⁴ A man, forty-three years of age, came to the clinic in 1939 complaining of loss of weight, ease of fatigue, weakness and intolerance of heat of six months' to one year's duration. In addition.

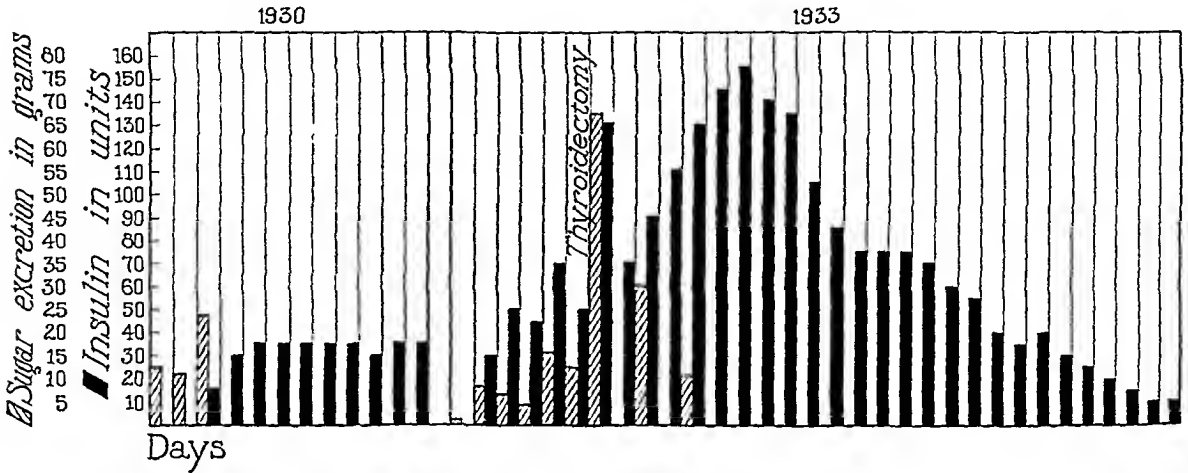


FIG. 2. The marked increase in severity of diabetes after surgical trauma is well shown. (Case III.)

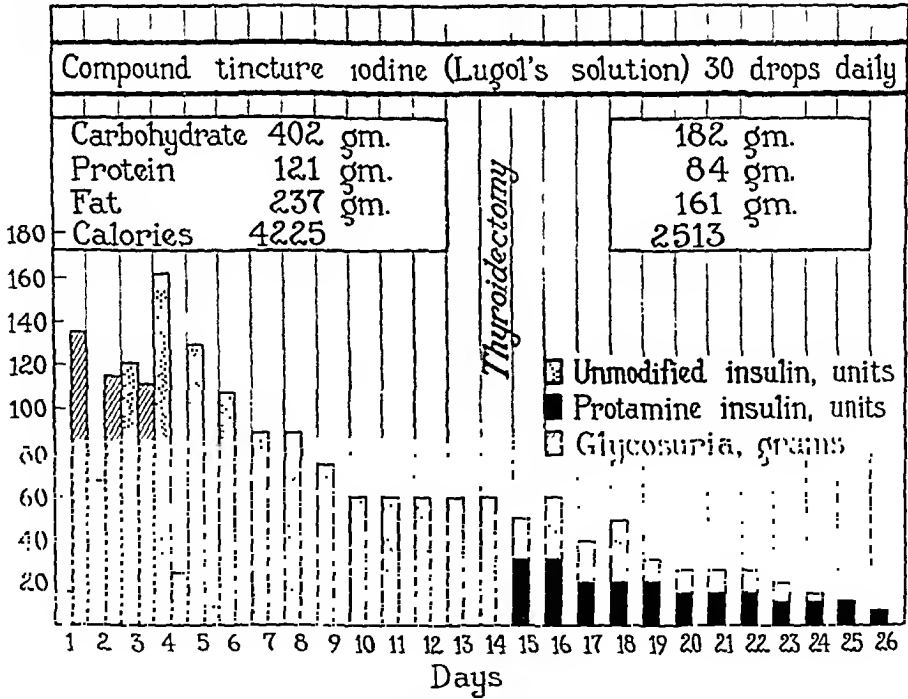


FIG. 3. Graphic illustration of the amelioration of the diabetic state by control of hyperthyroidism by the administration of strong iodine solution and thyroidectomy. (Case IV.) (From McDONOUGH, F. E., HAINES, S. F. and KEPLER, E. J.⁴)

diabetes then became milder and by the time of her dismissal, twenty-seven days after operation, five units of regular insulin before breakfast and five units before supper sufficed to keep her urine free of sugar.

for six months before admission polyuria and polydypsia had been present. A diagnosis of diabetes mellitus had been made and treatment with diet had been started. The patient also gave a history of thyroidectomy for exophthalmic

goiter in 1935 with good relief of symptoms. At the time of his admission to the clinic the value of the blood sugar was 278 mg. per 100 cc. and his basal metabolic rate was +23 per cent. Diffuse enlargement of the thyroid was noted. Diagnoses of recurrent exophthalmic goiter and diabetes mellitus were made and the patient was hospitalized for treatment.

On the second day of hospitalization 160 units of regular insulin were required and only partial control of the glycosuria was obtained. As is shown in Figure 3, in spite of this large amount of insulin 110 Gm. of glucose was excreted in the urine. Strong iodine solution was administered and the basal metabolic rate dropped to +7 per cent and the amount of insulin required dropped to 60 units daily. Control of the diabetes continued to be good after operation and eleven days later only 10 units of protamine zinc insulin were needed for control of the glycosuria. One month after dismissal the patient was able to discontinue the taking of insulin entirely without the reappearance of sugar in his urine.

The patients in Cases II and III had had diabetes for some time before the onset of hyperthyroidism. In each case control of the diabetes had been relatively easy. However, with the metabolic stress of hyperthyroidism the diabetes became more severe. The patient in Case IV noted onset of the diabetes after hyperthyroidism had been present for some time. Partial control of the diabetes did not ameliorate the symptoms of fatigue and weakness. After operation all three patients showed a marked reduction in the amount of insulin required. In addition, the first two patients illustrate the increase in severity of diabetes which is usually seen for a short period after thyroidectomy when this combination of diseases is present.

Diabetes Mellitus and Myxedema. A decrease in thyroid function may produce effects on diabetic patients, the opposite of those seen with excess thyroid, that is, the diabetes may be ameliorated to some degree. However, the changes are not usually striking. Myxedema in non-diabetic persons may produce an increased tolerance to glucose administered orally. This effect

is due in part to decreased rate of absorption from the gastrointestinal tract and, also, to decrease in general metabolism. Total lack of thyroid hormone would theoretically be helpful in controlling severe diabetes, and this has been attempted in at least one case (Case VI). Some of the effects of myxedema on human diabetes are illustrated in the following cases.

CASE V. A man, fifty-nine years of age, came to the clinic in July, 1941. His main symptoms were related to coronary sclerosis with rather frequent attacks of angina pectoris. Diabetes mellitus had been discovered two weeks previously. On physical examination it was found that the patient had a low-lying adenomatous goiter and persistent tachycardia. The basal metabolic rate was +20 per cent. The value for blood sugar was 242 mg. per 100 cc. The diabetes was brought under fair control by diet and a mixture of 6 units of protamine zinc insulin and 18 units of regular insulin daily before breakfast. He was given strong iodine solution, 10 drops three times daily, and sent home to return in a month for thyroidectomy. During this period the diabetes was under good control although he still needed 24 units of insulin mixture a day.

Upon his return to the clinic thyroidectomy was performed and the pathologic report was multiple adenomas in a gland showing parenchymatous hypertrophy. There was rather marked intensification of the diabetes the first few days after operation, and 140 units of insulin were required on the fourth postoperative day. The amount of insulin required dropped rapidly thereafter. When the patient was dismissed three weeks after operation, the basal metabolic rate was -21 per cent. There were no clinical signs of myxedema.

At home his insulin requirement continued to drop and two months after operation he was taking a mixture of only 6 units of protamine zinc and 4 units of regular insulin. With this dose he was having mild insulin reactions. The insulin was soon stopped altogether and he continued to be aglycosuric. In addition, rather frank signs of myxedema had developed. He returned to the clinic a few weeks later complaining of dry skin, sluggishness, fatigue and intolerance to cold. The basal metabolic rate was still -21 per cent. The concentration of cholesterol in the blood was 450 mg. per 100 cc.

The value for blood sugar was 170 mg. per 100 cc. and there was no sugar in the urine. Treatment with 1 gr. (0.065 Gm.) of desiccated thyroid was begun but the patient was unable to stay in Rochester for observation. When he was next seen three years later, the diabetes was well controlled by 12 to 18 units of a mixture of insulin and the myxedema was controlled by desiccated thyroid. The basal metabolic rate was +1 per cent.

CASE VI. This is the report of a patient who underwent total thyroidectomy in the hope of making his severe diabetes easier to manage. The case has been reported in detail by Wilder, Foster and Pemberton,⁵ and is included here only because it illustrates so well the effect of myxedema on diabetes. The patient, a white man twenty-six years of age, was first seen at the clinic in 1933. Diabetes mellitus had been present for eleven years. In spite of a rigid diet and 45 units of regular insulin daily there was considerable difficulty in controlling glycosuria, and insulin reactions occurred fairly frequently. There were no signs or symptoms of thyroid dysfunction and two basal metabolic rates were +5 and +2 per cent. Fasting blood sugar measured 429 mg. per 100 cc. and the concentration of cholesterol in the blood was 208 mg. per 100 cc. On a weighed diet of 2,300 calories, containing 103 Gm. of carbohydrate, and a dose of 30 units of insulin per day, the patient before operation excreted an average of 36 Gm. of carbohydrate daily in his urine.

The patient was aware of the hazards of total thyroidectomy and the uncertainty of the results that might be obtained. At operation 10 Gm. of histologically normal thyroid tissue was removed. Some tissue was preserved at the hilus of each lobe but the amount was not more than the size of a split pea. The parathyroid glands were not disturbed. The insulin requirement rose to 65 units on the fourth postoperative day. On this day 20 Gm. of glucose were excreted in the urine and the intake was 84 Gm. Thereafter the insulin requirement dropped gradually and thirty days after operation the urine was practically free of sugar on 15 units of insulin while the diet was the same as before operation. The basal metabolic rate at this time was -29 per cent.

While at home the patient kept an accurate account of the amount of sugar in the urine and insulin taken. Ten units was the average dose

which was necessary to keep his urine free of sugar.

Symptoms of myxedema appeared about sixty days after operation and 3 gr. (0.2 Gm.) of desiccated thyroid were given daily for a period of four days. The symptoms of myxedema began to regress but the insulin required on the fourth day was 30 units. Administration of desiccated thyroid was then stopped and two weeks later 10 units of insulin again kept the urine free of sugar. Thirty days later symptoms of myxedema reappeared. Three and a half months after operation the patient returned to the clinic and presented typical signs and symptoms of myxedema. The daily insulin requirement varied from eight to twelve units. The basal metabolic rate was -35 per cent. Control of myxedema, as far as gross evidence was concerned, was obtained on $\frac{1}{2}$ gr. (0.032 Gm.) of desiccated thyroid daily although the basal metabolic rate did not rise appreciably. On this dose the diabetes was controlled with 14 to 16 units of insulin. The patient was reasonably comfortable but felt that he was not as well generally as he had been with only the diabetes to concern him.

Case v illustrates the effect of both hyperfunction and hypofunction of the thyroid on diabetes. Diabetes became manifest after hyperthyroidism had been present for some time. After thyroidectomy the diabetes became much less severe and, with the development of myxedema, small doses of insulin produced insulin reactions. Insulin was again needed when the myxedema was controlled although never in amounts equal to those required when hyperthyroidism was present.

Case vi is included to illustrate the effect of a complete lack of thyroid hormone on diabetes. As can be seen, myxedema in this patient produced marked amelioration of the diabetes and control of the myxedema resulted in an increase in the severity of the diabetes.

ADRENAL CORTEX AND HUMAN DIABETES

Co-existing Diabetes Mellitus and Adrenal Cortical Insufficiency (Addison's Disease). Ablation of the adrenal glands from animals is followed by a decrease of the concentra-

tion of carbohydrate in the blood, liver and muscle. Hypoglycemia during fasting is a common manifestation of adrenal cortical insufficiency in some species, including the human being. Conversion of protein to carbohydrate is impaired. The rate of oxidation of administered glucose may be accelerated. Sensitivity to insulin may be strikingly increased. The rate of absorption of glucose from the intestinal tract is decreased.

The aforementioned effects of adrenalectomy are strikingly illustrated in the diabetic animal. There is marked amelioration of the diabetic state similar to that produced by hypophysectomy. Excretion of glucose, nitrogen and ketone bodies diminishes. Sensitivity to insulin is augmented. The full intensity of diabetes can be restored by administration of suitable amounts of adrenal cortical hormones which have carbohydrate activity, such as compound E (17-hydroxy-11-dehydrocorticosterone) or compound F (17-hydroxycorticosterone).

The foregoing physiologic principles can be applied in varying degrees to patients who have co-existing Addison's disease and diabetes mellitus, as illustrated by the following case reports.

CASE VII. The patient was first examined at the clinic in October, 1942, when she was thirty-seven years of age. A paternal uncle had diabetes. At the age of fifteen years she had been treated medically for thyrotoxicosis. At the age of twenty years she had experienced an attack of acute pelvic inflammatory disease.

In 1934, at the age of twenty-nine years, she had been found to have diabetes mellitus. She had severe diabetic acidosis at the time the diagnosis was made. For the next several years she took from 30 to 40 units of insulin daily, with fair to poor control of glycosuria. Pigmentation of the hands, face and neck was first noted by the patient and members of her family in 1939. Early in 1942 she began to note failure of strength and appetite. Soon she began to experience nausea, occasional vomiting, hiccup and abdominal distress. Insulin reactions, which had formerly been infrequent, occurred almost daily. In June, 1942, it was suspected by her physicians that she might have Addison's disease

in addition to diabetes mellitus, and she was treated with injections of desoxycorticosterone acetate. She continued to have insulin reactions and the daily dose of insulin was gradually decreased. In September, 1942, the administration of insulin was discontinued entirely. The urine remained consistently free of sugar.

In the initial examination at the clinic the blood pressure was 64 mm. of mercury systolic and 40 mm. diastolic. She was weak and nauseated. Pigmentation characteristic of Addison's disease was present. There were large areas of vitiligo on the arms. The urine was free of sugar and the value of the blood sugar was 40 mg. per 100 cc. The concentration of sodium in the serum was 128.7 mEq., chlorides 90.9 mEq. and potassium 5.1 mEq. per L.

Emergency treatment with intravenous infusions of solutions of sodium chloride, glucose and adrenal cortical extract resulted in simultaneous clinical improvement and reappearance of glycosuria and hyperglycemia.

Subsequent investigations gave the following results: The urinary excretion of 17-ketosteroids was 0.6 mg. in twenty-four hours. Results of a water test (Robinson, Power and Kepler) were positive in parts I and II. Repeated determinations of the serum sodium and chlorides under varying circumstances gave values as low as 119 mEq. per L. for sodium and 88 mEq. per L. for chloride. The values for serum potassium and blood urea were, for the most part, within normal limits. The value of blood sugar on numerous occasions and under varying conditions of therapy varied from 40 to 492 mg. per 100 cc. The daily urinary excretion of glucose varied from 0 to 142 Gm. Examination of the ocular fundi revealed a mild central punctate type of diabetic retinopathy.

The patient was observed in the hospital on five different occasions between October, 1942, and October, 1945. When she was treated for adrenal insufficiency with desoxycorticosterone acetate alone, she exhibited unusual sensitivity to insulin. On one occasion she experienced a severe hypoglycemic reaction eight hours after receiving 4 units of insulin. On another occasion she experienced an insulin reaction three hours after the administration of 3 units of insulin. On several other occasions she had hypoglycemic reactions without having received insulin, particularly if food was withheld for more than a few hours.

On the other hand, when her adrenal insufficiency was treated with large doses of whole adrenal cortical extract, hog adrenal extract (lipoadrenal cortex) or 17-hydroxy-11-dehydrocorticosterone (compound E), glycosuria increased and she was able to take as much as

the concentration of blood sugar was sustained at a high level, glycosuria was marked, ketonuria was intense and excretion of nitrogen was significantly increased. In another study, not illustrated in Figure 4, definite effects similar to those obtained with compound E were observed

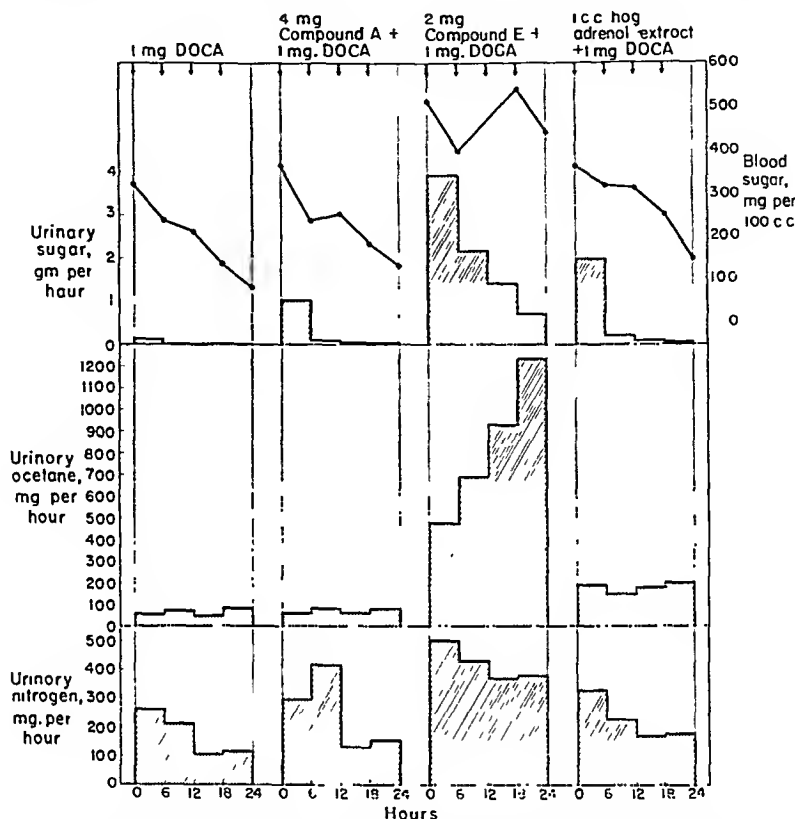


FIG. 4. Effects of 17-hydroxy-11-dehydrocorticosterone (compound E) compared to those of desoxycorticosterone acetate, 11-dehydrocorticosterone (compound A) and an extract of hog adrenal glands in Case VII. In each instance the hormone being studied was added to a basal treatment with desoxycorticosterone acetate. Data for blood sugar and urinary sugar, acetone and nitrogen during a period of fasting of twenty-four hours after withdrawal of insulin are shown.

44 units of regular insulin daily in 2 doses without experiencing symptoms of hypoglycemia.

Observations of the influence of various programs of treatment for adrenal insufficiency on the behavior of the diabetes were made during periods of fasting after withdrawal of insulin while the deficiency of salt and water of Addison's disease was controlled with desoxycorticosterone acetate. (Fig. 4.) When insulin was not administered and she fasted during treatment with desoxycorticosterone acetate, compound A or hog adrenal extract in the doses shown, the amount of sugar in the blood and urine decreased and only slight ketonuria was present. By contrast, during treatment with compound E

when a larger dose of hog adrenal extract was employed.

In December, 1945, the patient became ill at home and was thought to have pelvic peritonitis. At that time her adrenal insufficiency was apparently well controlled with hog adrenal extract and desoxycorticosterone acetate, as she was in diabetic acidosis in spite of taking 20 units of regular insulin daily. She died with hyperpyrexia and clinical findings suggestive of pulmonary edema.

At necropsy, the principal findings were pelvic peritonitis secondary to bilateral pyosalpinx, and atrophy of the adrenal cortices. No cortical cells could be seen in sections of the adrenals. The

pancreas weighed 25 Gm. and grossly presented evidence of fatty infiltration. On microscopic examination the islets showed no pathologic change.

CASE VIII. A woman, thirty years of age, was hospitalized on admission to the clinic, June 29,

had taken 20 to 30 units of protamine zinc insulin daily, and had noted a progressive failure of strength and a gradual increase in the frequency and severity of hypoglycemic reactions. In April, 1946, she had first become aware of increased pigmentation of the face and hands.

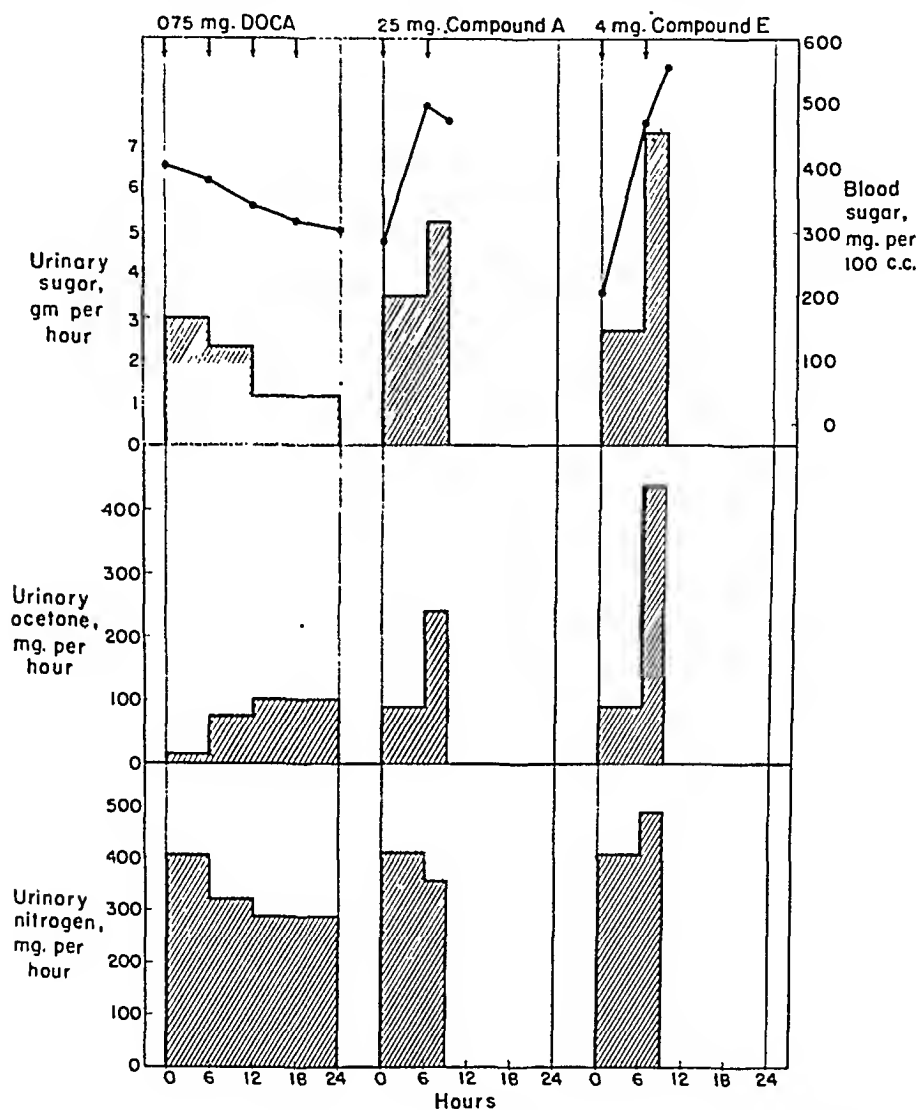


FIG. 5. Comparative effects of desoxycorticosterone acetate, 11-dehydrocorticosterone (compound A) and 17-hydroxy-11-dehydrocorticosterone (compound E) in Case VIII. Data for blood sugar and urinary sugar, acetone and nitrogen during a period of fasting after withdrawal of insulin are shown. In the latter two studies, involving the use of compound A and compound E, it was necessary to terminate the observations after nine hours of fasting because of the development of severe ketosis.

1946. In June, 1945, she had consulted her physician because of thirst, polyuria, weakness and loss of weight and had been found to have diabetes mellitus. Weakness had been an unusually prominent symptom at that time. The urine became free of sugar when she took 30 units of protamine zinc insulin daily for a week. It remained free of sugar without the use of insulin until October, 1945, when she had a sore throat and glycosuria recurred. Since then she

On admission to the hospital the patient presented evidences of both adrenal insufficiency and uncontrolled diabetes. The blood pressure was 90 mm. of mercury systolic and 50 mm. diastolic. She was profoundly weak and nauseated and hiccupped at frequent intervals. There was frank addisonian pigmentation of moderate degree. The urine contained sugar, grade 4, but no acetone or diactic acid. The value for blood sugar was 289 mg. per 100 cc. The serum sodium

was 126 mEq., chlorides 97.3 mEq., potassium 6.8 mEq., carbon dioxide content 24.2 mEq. per L. and the blood urea 40 mg. per 100 cc.

Subsequently additional data confirming the presence of Addison's disease were obtained. The urinary excretion of 17-ketosteroids varied between 0.5 and 1.5 mg. per twenty-four hours on several occasions. A differential count of leukocytes showed 47 per cent lymphocytes with a total count of 6,200 per cubic millimeter. Results of a water test (Robinson, Power and Kepler) were strongly positive in parts I and II. A salt-deprivation test (Cutler, Power and Wilder) had to be terminated twelve hours after it was started because of symptoms of acute adrenal insufficiency, which were promptly corrected by an intravenous infusion of solution of sodium chloride and adrenal cortical extract. A tuberculin test gave negative results.

Studies of the influence of various programs of treatment for Addison's disease on the behavior of the diabetes during periods of fasting after withdrawal of insulin, similar to the studies which had been carried out previously in Case VII, were made. During treatment with desoxycorticosterone acetate the concentration of blood sugar decreased during fasting, and glycosuria and ketonuria were of only moderate intensity. (Fig. 5.) By contrast, when Addison's disease was treated with 11-dehydrocorticosterone (compound A) or 17-hydroxy-11-dehydrocorticosterone (compound E), the diabetes was greatly intensified. In each instance severe ketosis developed within the first nine hours of fasting after withdrawal of insulin, so that it was necessary to terminate the observation and administer insulin and infusions of solutions of sodium chloride. The effects of 4 mg. of compound E every six hours appeared to be somewhat more marked than those of 25 mg. of compound A every six hours.

After the metabolic studies which have been described the patient was permitted to return home. She was in good condition taking 2 doses of regular insulin daily totaling 28 units, 1 mg. of desoxycorticosterone acetate, 1 cc. of hog adrenal cortical extract and 3 Gm. of sodium chloride in addition to that contained in her food. She died at home on February 14, 1947, several days after a severe hypoglycemic reaction.

The history in each of the foregoing cases indicated some amelioration of diabetes

with the onset of adrenal cortical insufficiency. In Case VII the amelioration was marked, so that insulin was no longer necessary for control of glycosuria and, indeed, hypoglycemic reactions occurred even though insulin had not been administered. In Case VIII, on the other hand, the amelioration of the diabetes was less marked, suggesting that the patient might have had a functioning remnant of adrenal cortical tissue which was producing a sufficient supply of carbohydrate-active steroid hormones to maintain a moderately severe diabetic state.

The metabolic studies in each case indicate that the diabetic state could be greatly intensified by the administration of carbohydrate-active adrenal steroids but not by the administration of desoxycorticosterone acetate alone.

Diabetes Mellitus Associated with Hyperfunctioning Lesions of the Adrenal Cortex. Diabetes mellitus which is sometimes observed in the case of patients who have hyperfunctioning lesions of the adrenal cortices is in all likelihood due to excessive production of adrenal cortical hormones which have predominant carbohydrate activity, that is, the 11 and 11-17 oxygenated steroids. The most potent of these are 17-hydroxy-11-dehydrocorticosterone (compound E) and 17-hydroxycorticosterone (compound F), the latter having slightly stronger effects than the former.

Ingle and his associates⁶⁻⁸ have produced the counterpart of human "steroid diabetes" in rats by the administration of relatively large doses of compound E or compound F. The diabetic state which is so produced has certain characteristics which differ from those of the diabetes which is commonly observed in children and young adults. (1) It is relatively insensitive to insulin, Ingle and associates having failed to control glycosuria completely in some of their rats with as much as 1,000 units of insulin daily. (2) It becomes mild when food is withheld so that glycosuria disappears. (3) Since one of the effects of the adrenal hormones which cause this type of diabetes is to stimulate the

formation of sugar from protein, it is associated with a negative nitrogen balance, even when glycosuria is minimal or absent.

The following two cases seem to be examples of "steroid diabetes" in human beings.

CASE IX. This case has previously been reported in detail by Sprague, Pricstley and Dockerty.⁹ A woman, forty-nine years of age, came to the clinic for examination in February, 1941. A diagnosis of diabetes mellitus had been made three years previously and the condition had been treated with insulin in doses up to 145 units daily. Hypoglycemic reactions had never occurred.

Physical examination was negative except for a large, deep, movable mass in the right upper quadrant of the abdomen. The blood pressure was 160 mm. of mercury systolic and 94 mm. diastolic. The habitus was normal, the amount and distribution of hair on the body were normal, and except for atrophic changes in the vulva and vagina, there were no abnormalities of the external genitalia or pelvic organs. The menstrual history was normal and she was still menstruating regularly. Laboratory examinations were negative except for glycosuria and a fasting blood sugar which measured 252 mg. per 100 cc.

During several days of study before surgical exploration of the abdominal mass the patient received each morning a combined dose of protamine zinc and regular insulin totaling between 30 and 68 units. As much as 28.7 Gm. of glucose were excreted in the urine in twenty-four hours. Ketone bodies were never found in the urine. There were no hypoglycemic reactions.

Surgical exploration of the abdomen was performed on March 12, 1941. A tumor of the right adrenal cortex weighing 1,550 Gm. was removed. Histologic examination revealed that the lesion was an adenocarcinoma, grade 2.

After the day of operation the urine remained consistently free of sugar. On the fifth post-operative day the value of blood sugar was 88 mg. per 100 cc. The dose of insulin was gradually reduced and it was discontinued on the sixteenth postoperative day.

All subsequent investigations of the patient's carbohydrate metabolism gave normal results. There was never any further evidence of diabetes. A glucose tolerance test performed eight months after removal of the tumor gave a

normal result. Determinations of the fasting blood sugar at intervals up to eight years after the operation were all normal.

CASE X. A boy, fifteen years of age, came to the clinic on February 3, 1948, because of diabetes mellitus associated with weakness and loss of weight. Diabetes had been discovered in January, 1946. At that time it was also noted that his face was redder and rounder than formerly and pink striae had been observed on the thighs. Insulin was employed from that time until June, 1946.

From June, 1946, to December, 1947, there was a complete remission of the diabetes. The abnormal redness and contour of the face also disappeared. In December, 1947, symptoms of diabetes, associated with redness and roundness of the face and marked weakness, reappeared. Glycosuria was again found, and insulin in doses up to 80 units daily was once more employed. Even with this dose of insulin, glycosuria persisted and there were no insulin reactions.

Physical examination on admission of the patient to the clinic revealed most of the classical features of Cushing's syndrome, including hypertension, weakness, a full, round face of high color, acne, dry skin, keratosis pilaris, purplish striae, protuberant abdomen and a wasting of the arms and legs. Laboratory and roentgenologic studies disclosed hypochloremic, hypokaliemic alkalosis of marked degree, osteoporosis, lymphopenia, glycosuria and hyperglycemia. The fasting blood sugar was 245 mg. per 100 cc. The urinary excretion of 17-ketosteroids was 77.5 mg. in twenty-four hours, the beta fraction being 18.5 per cent. The urinary excretion of corticosteroids was 17.1 mg. in twenty-four hours. The latter finding eventually led to the isolation of 17-hydroxycorticosterone (compound F) from the urine, 191 mg. of purified hormone being obtained from a twenty-five-day collection of urine.¹⁰

The clinical diagnosis was Cushing's syndrome associated with diabetes mellitus.

Metabolic studies¹¹ disclosed the following significant points: (1) The diabetes was severe and relatively insensitive to insulin, glycosuria being incompletely controlled with doses of insulin ranging from 20 to 130 units daily. (2) Balances for nitrogen, calcium and phosphorus were negative. (3) Glycosuria virtually disappeared during fasting even though insulin was withheld.

The death of the patient after surgical resection of the right adrenal gland, which was hyperplastic, precluded further metabolic study. At necropsy, markedly hyperplastic adrenal cortices were found, the remaining portion of the right adrenal gland weighing 5 Gm and the left adrenal, 29 Gm.

The foregoing two cases are presumably instances of "steroid diabetes" in man, analogous to that produced by Ingle and co-workers in rats by the administration of large doses of carbohydrate-active adrenal steroids. The evidence in support of this analogy was particularly strong in Case x, for 17-hydroxycorticosterone (compound F), an adrenal steroid hormone known to have strong carbohydrate activity, was isolated from the urine in considerable quantities.¹⁰ Furthermore, the diabetes in this case was shown to have the characteristics of "steroid diabetes" in animals; namely, insensitivity to insulin, negative nitrogen balance even when glycosuria was minimal and mildness during fasting.

In Case ix the evidence that the diabetes was due to excessive production by the adrenal cortical tumor of hormones which have carbohydrate activity, rather than to primary insulin deficiency, was also strong. All evidences of diabetes disappeared soon after removal of the tumor, just as it does in rats with steroid diabetes when the administration of the diabetogenic adrenal steroid is interrupted. It can therefore be reasonably presumed in this case that the diabetes was due solely to overproduction of carbohydrate-active adrenal steroids, and that islet function was basically within normal limits.

SUMMARY

As is true in the experimental animal, the behavior of diabetes mellitus in the human may be markedly altered by either hypofunctioning or hyperfunctioning lesions of the anterior pituitary, thyroid or adrenal cortex. In general, hypofunctioning lesions of these glands of internal secretion ameliorate existing diabetes while hyperfunctioning lesions intensify it. Hyperfunction of the anterior pituitary due to eosinophilic ade-

noma, or of the adrenal cortex due to tumor or hyperplasia may apparently be the sole cause of diabetes in rare cases.

Ten cases in which diabetes mellitus was associated with hypofunctioning and hyperfunctioning lesions of the aforementioned glands have been presented. The basic physiology concerned in the alteration of the diabetic state by such lesions has been considered briefly. It is emphasized that the observations which were made in these cases are not applicable to the majority of cases of diabetes, in which evidences of endocrine disease other than the diabetes itself are usually absent.

REFERENCES

1. HOUSSAY, B. A. and BIASOTTI, A. La diabetes pancreática de los perros hipofisoprivos. *Rev. Soc. argent. de biol.*, 6, 251, 1930.
2. YOUNG, F. G. Permanent experimental diabetes produced by pituitary (anterior lobe) injections. *Lancet*, 2, 372, 1937.
3. ALMY, T. P. and SHORR, EPHRAIM. Disappearance of diabetes mellitus associated with acromegaly following acute mastoiditis and basilar meningitis (Abstr.). *J. Clin. Endocrinol.*, 7, 455, 1947.
4. McDONOUGH, F. E., HAINES, S. F. and KEPLER, E. J. Treatment of hyperthyroidism complicated by diabetes. *Proc. Staff Meet., Mayo Clin.*, 16, 599, 1941.
5. WILDER, R. M., FOSTER, R. F. and PEMBERTON, J. DEJ. Total thyroidectomy in diabetes mellitus. *Endocrinology*, 18, 455, 1934.
6. INGLE, D. J., SHEPPARD, RUTH, EVANS, J. S. and KUIZENGA, M. H. A comparison of adrenal steroid diabetes and pancreatic diabetes in the rat. *Endocrinology*, 37, 341, 1945.
7. INGLE, D. J. The Production of Experimental Glycosuria in the Rat. In PINCUS, GREGORY. Recent Progress in Hormone Research, the Proceedings of the Laurentian Hormone Conference Vol. 2, pp. 229-253. New York, 1948. Academic Press, Inc.
8. INGLE, D. J. The production of glycosuria in the normal rat by means of 17-hydroxy-11-dehydrocorticosterone. *Endocrinology*, 29, 649, 1941.
9. SPRAGUE, R. G., PRIESTLEY, J. T. and DOCKERTY, M. B. Diabetes mellitus without other endocrine manifestations in a case of tumor of the adrenal cortex. *J. Clin. Endocrinol.*, 3, 28, 1943.
10. MASON, H. L. and SPRAGUE, R. G. Isolation of 17-hydroxycorticosterone from the urine in a case of Cushing's syndrome associated with severe diabetes mellitus. *J. Biol. Chem.*, 175, 451, 1948.
11. SPRAGUE, R. G., HAYLES, A. B., MASON, H. L., POWER, M. H. and BENNETT, W. A. "Steroid diabetes" associated with Cushing's syndrome and excretion of 17-hydroxycorticosterone (compound F) in urine, metabolic studies. *J. Lab. & Clin. Med.*, 33, 1472, 1948.

Pregnancy Complicating Diabetes^{*}

PRISCILLA WHITE, M.D.

Boston, Massachusetts

DURING the past fifteen years a study has been made at the George F. Baker Clinic of the New England Deaconess Hospital to determine possible causes and the means to prevent the high fetal wastage in diabetic pregnancies. The following report is a summary of the experiences with 439 viable diabetic pregnancy cases in which assays for one or more of the sex hormones of pregnancy were determined. Viability in the infant was defined by weight, namely, in excess of 960 Gm. This series of 439 includes all consecutive cases under personal observation. Excluded from the report are consultation cases treated elsewhere and patients reporting to the clinic for delivery but arriving too late for significant studies for sex hormone excretion.

The series appears to be unique because it is characterized by the number of primiparae, the number of patients in whom the onset of diabetes occurred in childhood and youth and those in whom the duration of diabetes is long. Primiparae numbered 57 per cent of the series. The onset of diabetes had occurred under the age of twenty years in more than half (58 per cent) and the duration was long, exceeding ten years in 50 per cent.

Although maternal mortality was low, for there was only one death or a case mortality of 0.2 per cent, fetal fatalities numbered 78, or 18 per cent. The maternal death was technically so classified only. It occurred fifty days after delivery and was proved by autopsy to be due to infectious hepatitis. These vital statistics as well as those reported elsewhere indicate that fetal not maternal survival constitutes the problem when pregnancy complicates diabetes.

Abnormalities in the obstetric course were common and included eclampsia four times (1 per cent); an additional seventy-six patients (17 per cent) had hypertension and albuminuria; eighty (18 per cent) had hypertension alone and thirty-four (8 per cent) albuminuria alone. Nearly one-half the number thus had evidence of hypertensive disorders or renal disease. Placenta previa occurred once; premature rupture of membranes before the twentieth week with continuous loss of amniotic fluid for weeks and months occurred four times. Two other deviations from normal obstetric courses were frequently seen, namely, irritability of the uterus and hydramnios. These complications occurred in varying degrees in nearly all patients.

Diabetic crises, on the other hand, were infrequent. Coma, defined as a lowering of the CO₂ content of the blood to 9 m.Eq., occurred in eight patients only, or 2 per cent, and hypoglycemia of severity in four, or 1 per cent.

The fetal fatalities are summarized in Table I. Of the seventy-eight fetal deaths, thirty-four were stillbirths and forty-four occurred in the early neonatal period. From Table I it appears that fetal fatalities have been influenced in varying degrees by (1) poor control of maternal diabetes, (2) the occurrence of congenital fetal defects, (3) the degree of maternal vascular disease, (4) prematurity, (5) duration of diabetes, (6) its age of inception and (7) the imbalance of the sex hormones of pregnancy.

Diabetic coma which may be taken as the measure of the maximum degree of poor control of diabetes coincided with 5 per cent of the fetal fatalities. Indeed, only two infants in this series survived a bout of dia-

^{*} From the George F. Baker Clinic, New England Deaconess Hospital, Boston, Mass.

betic coma. The harmful influence appeared to be more in relation to the occurrence of stillbirths than it did to neonatal deaths, for it coincided with intrauterine fetal death in 10 per cent of such cases. In only 2 per cent of the neonatal deaths was a bout of

TABLE I

RELATIVE FREQUENCY OF CONDITIONS ASSOCIATED WITH SEVENTY-EIGHT FETAL DEATHS

	Per cent
A. Total:	
Eclampsia	1
Diabetic coma.	5
Congenital anomalies	9
Arteriosclerosis	
Pelvic	20
Total . . .	33
Hypertension and/or albuminuria	46
Prematurity	46
Long duration of diabetes (more than 10 years)	52
Early age at onset of diabetes (under 10 years)	66
Imbalance of sex hormones	97
B. Comparison of Relative Frequency of Conditions Associated with Fetal Deaths Classified As Stillbirths and Neonatal Deaths:	

	Stillbirths Per cent	Neonatal Deaths Per cent
Eclampsia	0	2
Coma	10	2
Congenital anomalies	3	15
Arteriosclerosis		
Pelvic	24	16
Total . .	33	42
Hypertension and/or albuminuria	71	52
Prematurity	32	66
Long duration of diabetes	73	37
Early age at onset of diabetes	74	60
Sex hormonal imbalance	100	97

coma coincidental with the fatality. The reverse situation, hypoglycemia of severity, did not coincide with fetal fatalities. Convulsive episodes, one in an epileptic and the other during the administration of lithium salt substitute, coincided with an intrauterine death each.

The most tragic of the harmful influences—tragic because it is unpredictable—is the occurrence of the congenital fetal defect. This coincided with 8 per cent of the fetal fatalities. Only one defect, or 3 per cent, was demonstrated in a stillborn infant. The lethal defect in this infant was the absence

of both kidneys. Congenital anomalies coincided with 15 per cent of the neonatal deaths and included one instance each of hemorrhagic disease of the newborn, multiple skeletal defects and defect of the skull incompatible with survival, congenital heart, congenital pneumomediastinum and anencephaly.

The most devastating of the harmful effects because of its influence in early as well as in late pregnancy periods was the degree of maternal vascular disease. Some evidence of arteriosclerosis was found with 33 per cent of the fetal fatalities, 33 per cent of the stillbirths and 42 per cent of the neonatal deaths. When arteriosclerosis in the young diabetic had progressed so far that the pelvic blood vessels were calcified, the fetal survival for the entire period of pregnancy was 10 per cent only. In such a group, when everything which appears to promote successful outcome of diabetic pregnancies was carried out, the fetal survival in twenty-eight viable cases rose to 50 per cent. When the arteries of the pelvis are shown to be calcified by x-ray, involvement of the uterine and ovarian arteries is inferred. These are the first arteries in the body of the normal woman to undergo sclerotic changes and it would be unlikely that in the diffuse sclerosing process of the diabetic they would be expected. Although the calcification demonstrable by x-ray suggests the medial type of sclerosis, internal changes and occlusive vascular disease characteristic of diabetes are also inferred. No uteri in this series of patients have been observed at the time of delivery. Hysterectomies have not been performed and the one patient who came to autopsy fifty days after delivery did not have calcified pelvic arteries. The most striking case in this group is that of E. R., Case 1469, who died at the age of forty in December, 1948. Her death due to arteriosclerotic cardiovascular disease occurred after thirty years of diabetes. Pregnancies had occurred ten years, eight years and six years prior to death. The first pregnancy terminated successfully in a living birth and the

child is well today. On autopsy the endometrium, myometrium and the arteries were described as those of a woman of seventy years of age.

The importance of the vascular problem in obstetric diabetes cannot be overemphasized. A survey of our former diabetic children, defined as patients in whom the onset of diabetes occurred under the age of fifteen, who then survived twenty years or more of diabetes, showed that 93 per cent had some evidence of vascular disease. Such lesions do not become manifest often under the age of twenty years and are rare when diabetes is of less than ten years' duration. The specificity of the site of the attack in those in whom the disease starts in childhood is of great importance in the obstetric problem because destructive effects are seen in the retina and in the kidneys most commonly. (Table II.)

Hypertension and albuminuria, or hypertension alone or albuminuria alone, coincided with 46 per cent of the fetal fatalities and prematurity coincided with 46 per cent. In only 29 per cent of the stillbirths was evidence of hypertension or albuminuria lacking and 71 per cent of the cases had such abnormalities. To a lesser degree, but also in half the cases, hypertension, albuminuria or both were associated with neonatal deaths. Of greatest importance from the viewpoint of the obstetric and medical management of the patient was the fact that 68 per cent of the stillbirths occurred late in pregnancy, from the thirty-sixth to the fortieth week, whereas only 34 per cent of the neonatal deaths occurred after the thirty-fifth week. Long duration of diabetes and early onset of the disease were associated with more than half of the fetal fatalities, namely, 53 and 66 per cent, respectively, the harmful influence being shown more in relation to stillbirths than to neonatal deaths.

The most frequent of the harmful influences, however, was the imbalance of the sex hormones of pregnancy, coinciding with 97 per cent of the fetal fatalities and occurring in 90 per cent of our entire series of

patients. The abnormalities included a rise of chorionic gonadotropin between the twenty-third and thirty-fifth week of pregnancy to a level of 200 rat units per 100 cc. of serum or above, a lowering of the excretion of estrogen with abnormal ratios of

TABLE II
DURATION OF DIABETES AND VASCULAR COMPLICATIONS

Duration of Diabetes (Years)	Retinal Arterio-sclerosis Per cent	Retinitis Per cent	Calcified Arteries Per cent	Nephritis Per cent
Under 10.....	3	3	3	2
10-14.....	10	10	8	6
15-19.....	50	45	40	30
20 and over....	85	75	70	40

Age in Years and Vascular Complications				
Age in Years				
Under 20....	8	2	5	2
20-29.....	60	50	50	30

the degradation products and lowered excretion of pregnanediol glucuronidates.

From the foregoing it is evident that our problem must concern the investigation of the causes and the means to prevent premature delivery of the infant of the diabetic mother prior to the period of its viability (which appears to be later than that of the normal woman) and, secondly, the termination of the pregnancy at the point of viability and before the dreaded late intra-uterine accident can occur.

In addition to the chemical grading of patients, which has been previously reported upon, in 1948 clinical grading of the obstetric diabetic patient was made. This evaluation was based upon the pre-pregnancy state and the designation was alphabetical, A through F. Classes A through E referred to fetal risk and F to maternal risk. From the previous discussion it is evident that age at onset of diabetes, duration, severity and degree of maternal vascular disease all influence the fetal survival unfavorably. Renal disease carries with it maternal hazards in the diabetic population

as well as the obstetric population at large. Therefore, the grading of the patients was as follows:

Class A, with highest chance for fetal survival, includes patients in whom the diagnosis of diabetes was made upon a

TABLE III
SUMMARY OF 433* CASES DIVIDED ACCORDING TO SEX
HORMONAL BALANCE

Sex Hormonal Balance	No. of Cases	Eclampsia Per cent	Hypertension and Albuminuria Per cent	Delivery Prior to 34th Week Per cent	Fetal Survival Per cent
Abnormal	89	3	26	17	58
Corrected	297	0.3	16	9	89
Normal...	47	0	6	0	95

* Cases of placenta previa—1; premature rupture of membranes—4; erythroblastosis—1 excluded.

glucose tolerance test which deviates but slightly from the normal. Such patients require no insulin and little dietary regulation. They numbered only 5 per cent of our 439 cases.

Class B (29 per cent of this series) included patients whose diabetes started in adult life at the age of twenty or above, and those in whom the duration of the disease was less than ten years and those who were free from vascular disease.

Class C (44 per cent of this series) included patients whose diabetes was of long duration, between ten and nineteen years, those in whom the onset of diabetes occurred between ten and nineteen years of age or those who had minimal vascular disease, such as retinal arteriosclerosis or calcification of the vessels of the legs alone.

Class D (14 per cent of the group) included patients whose diabetes was of twenty or more years' duration, or whose onset occurred under ten years or who had more evidence of vascular disease such as retinitis, transitory albuminuria or transitory hypertension.

Class E included patients in whom calcification of the pelvic arteries was demon-

strable by x-ray. They numbered 7 per cent of our series.

Class F (1 per cent) included all patients with nephritis.

In addition to the clinical classification the cases were divided as previously into three classes upon a chemical basis as follows: first, forty-seven cases in which no examination for chorionic gonadotropin exceeded 200 RU/100 cc. of serum between the twenty-third and the thirty-fourth week and/or in whom the pregnandiol excretion did not fall below the level of minimal normal excretion, according to the curve of Venning and Browne; second, eighty-nine cases which did show chemical evidence of abnormal balance of the sex hormones of pregnancy; third, 297 cases which received sex hormone treatment. The fetal survival of the two first groups, shown in Table III, was as follows: 58 per cent when the hormonal balance was abnormal and uncorrected and 95 per cent when the hormonal balance was spontaneously normal. With added duration of diabetes and the incidence of diabetic arteriolar nephrosclerosis, the evaluation of pre-eclampsia in the group has become difficult. Hypertension and albuminuria occurred in 26 per cent of the patients in whom the hormonal balance was abnormal and in 6 per cent of those in whom it was spontaneously normal, and spontaneous delivery before the thirty-fourth week occurred in 17 per cent of the patients in whom the hormonal balance was abnormal and in none of those in whom the hormonal balance was completely normal.

In order to prevent the high fetal wastage in obstetric diabetes, premature delivery and pre-eclampsia, the management suggested by the experience with the 439 cases includes, first, good treatment of diabetes; second, substitutional hormonal therapy; third, the correction of edema and hydramnios; fourth, premature delivery and, fifth, special care of the infant whose viability was obviously not that of the infant of the normal woman of comparable period of gestation and size.

The dietary prescription included calories adequate to meet the metabolic needs of mother and child, namely, 30 calories per Kg. of body weight throughout pregnancy. The protein intake was high, namely, 2 Gm. per Kg. of increasing body weight, and the carbohydrate liberal, from 180 to 250 Gm. daily. The fat was prescribed merely to complete the caloric prescription.

The plan for insulin therapy has been based upon the prevention of accidents resulting from the extreme glycosuria due to the low renal threshold. With nearly normal levels for blood sugar these women may excrete 100 to 150 Gm. of sugar in twenty-four hours. When utilization of glucose falls below 100 Gm., ketosis sets in easily. Attempts to correct glycosuria with single massive doses of insulin favor the development of severe hypoglycemic shock. In the past a basic dose of long-acting insulin has been administered before breakfast and supplemented by three or four additional doses of rapidly acting insulin before breakfast, before lunch, before supper and even at bedtime. Twenty-four patients were adjusted to modified protamine, NPH-50, insulin and of this number 60 per cent were successfully treated with a single dose in twenty-four hours.

The plan for hormonal therapy at present is influenced by our clinical as well as chemical classification. A wide variety of forms of estrogenic and progestational therapy have been employed. Natural and synthetic estrogens included stilboestrol, progynon B, benzeestrol and premarin. In a few patients oreton was used in place of progesterone. Administration has included oral route, parenteral injection and implantation of pellets. The duration of therapy has varied from three to thirty-two weeks. Adequate therapy is now defined as continuous and daily, certainly not less often than every second day.

From our experience the present plan for sex hormone therapy has been developed as shown in Table IV: Class A none, Classes B and C from 5 to 50 mg. of stilbestrol and proluton daily, Class D from 10 to 75,

Classes E and F from 25 to 125 mg. of each intramuscularly daily.

Therapy is started by choice as early as the sixth week and continued until the day before delivery. The husbands are taught the administration of the intramuscular

TABLE IV
SEX HORMONAL THERAPY IN MG. OF STILBESTROL AND
PROLUTON ACCORDING TO WEEKLY PREGNANCY
AND CLINICAL CLASSIFICATION

Week of Pregnancy	Stilbestrol and Proluton in mg. According to Class			
	A	B and C	D	E and F
6-19.....	0	5	10	25
20-23.....	0	10	15	50
24-27.....	0	15	25	75
28-31.....	0	25	50	100
32 and up.....	0	50	75	125

injections, for daily intramuscular injections of stilbestrol and progesterone are considered the most efficacious form of treatment. Deviations from normal hormonal excretion levels have been used as the guide for regulation of doses of therapy. Thus if the level for chorionic gonadotropin remained high and/or the excretion of pregnandiol low, the patient has been advised to advance her schedule to that of the next four-week period. Deviations from normal clinical course, such as abnormal gain in weight, edema, hydramnios, hypertension and/or albuminuria, have all been used as indications, too, for advancing therapy.

The effect of sex hormonal therapy upon fetal survival was most favorable. The survival rate rose from 58 to 89 per cent. Today it has become difficult to evaluate the hypertension and albuminuria seen in the long-duration young diabetic. Since 1940 every juvenile patient surviving fifteen years of diabetes and coming to autopsy at the Deaconess Hospital has shown intercapillary glomerulosclerosis. Pregnancy may merely reveal the latent form of vascular nephritis. However, it is our clinical impression that the typical pre-eclampsia

which was seen in the shorter duration cases prior to 1936 is seen today but rarely. The incidence of hypertension and albuminuria fell from 26 to 16 per cent and premature delivery before the thirty-fourth week from 17 to 9 per cent in the 297 patients treated continuously with substitutional hormonal therapy prior to the twentieth week.

Although no side reactions were observed, fifty consecutive patients treated with a special form of stilbestrol developed hyperplastic endometritis, requiring dilatation and curettage on one or more occasions and in some instances repeated blood transfusions.

In our experience the use of oral stilbestrol alone was unsatisfactory. Lack of absorption was feared. Each pregnancy in a diabetic after ten years' duration is a premium; therefore, those started with it were transferred usually to parenteral administration because of the frequent occurrence of abnormalities in the clinical and chemical course. When oral stilbestrol was administered, the dose range was from 25 to 350 mg. daily.

Supplementing hormone therapy and directed against the disturbance of water balance, manifested by edema and hydramnios, was the prescription of ammonium chloride in doses from 4 to 20 Gm. daily. (The latter was self-prescribed.)

Patients whose diets were relatively low in sodium, especially in sodium chloride, were advised through the omission of table salt, the use of fresh butter, salt-free breads and fresh vegetables. Sodium bicarbonate was forbidden.

The plan for delivery of the diabetic was influenced by our experience with stillbirths and our concept of diabetes and of the diabetic pregnancy. Rapid sex maturity is characteristic of diabetes in childhood. Rapid aging is characteristic of the disease in any period of life. This process of rapid maturity and rapid aging appears to be characteristic of the diabetic pregnancy. The large size of the fetus and the placenta, the fetal fat, growth of hair and nail development are all suggestive of the maturing process. The intrauterine death or the

premature termination of the pregnancy appears to be another manifestation of aging. The former may even be considered as comparable to gangrene in the young diabetic similar to the vascular changes in the eye and kidney. Since 68 per cent of the stillbirths occurred after the thirty-fifth week, premature delivery was elected. By the method of trial and error the thirty-eighth week was sought, but hypertension, albuminuria or progressive hydramnios are indications for an earlier delivery. Deviation from normal hormonal balance have not been used as guides for the timing of delivery.

Cesarean section has been elected if the cervix has not been effaced. In fact, such deliveries have been done in 68 per cent, and 32 per cent only of these patients were delivered by the normal route. Cesarean sections have been done under spinal anesthesia without preliminary medication. An infusion of 1,000 cc. of 10 per cent glucose in distilled water is administered preoperatively and again six to eight hours after delivery. If long-acting insulins are used, the last dose of insulin of any type in a planned delivery is given twenty-four hours prior to it. Normal deliveries are conducted under spinal anesthesia. Sedation is held to minimal levels of 3 gr. of seconal and $\frac{1}{100}$ gr. of scopolamine.

The care of the infant prenatally includes, when possible, the correction of those abnormalities in which the infant of the diabetic mother differs from the infant of the normal woman. The differences included the large size, icterus, respiratory embarrassment, instability of the blood sugar, splachnomegaly and excessive erythropoiesis of the liver and spleen.

In the past, 80 per cent of the infants of diabetic mothers exceeded the expected weight for the period of gestation. Irrespective of gestation period 68 per cent of the infants in this series weighed less than 8 pounds, 32 per cent more than 8 pounds, 15 per cent more than 9, and 7 per cent only more than 10 pounds. The large size of the infant appears to be contributed to by three

factors: (1) edema, (2) obesity and (3) the splenomegaly.

Instability of the blood sugar rather than true hypoglycemia appears to be characteristic of the infant who may show relative hyperglycemia at birth followed by precipitous fall of blood sugar in four hours to a level of 40 mg. or below and subsequently a spontaneous rise of blood sugar in another four hours. Congenital anomalies complicated 80 per cent of these infants but in only 10 per cent were they severe and in less than 2 per cent of the cases lethal defects occurred. Respiratory difficulty of the infant appears to be associated with an excess of fluid in the upper air passages and lungs. Better control of maternal diabetes to prevent obesity and instability of the infant's blood sugar, better control of the disturbed water balance by high protein diets, salt restriction, ammonium chloride and sex hormonal therapy, better control of hormonal imbalance to prevent the irritable uterus, premature delivery and pre-eclampsia have all been sought.

The postnatal handling of the infant has been reported in detail by Gellis, White and Pfeffer.¹ It is directed against the respiratory difficulty. The clinical picture of the first few hours after delivery of those infants not progressing satisfactorily is the following: At birth the infant usually cries well and vigorously. It appears to aerate satisfactorily but within one or two hours exhibits a complaining cry. Evidence of costophrenic and intercostal retraction are observed. Bouts of cyanosis, apnea and sweating follow, and death may ensue eighteen to thirty-six hours after delivery. Autopsies have shown little evidence for adequate cause of death except for the atelectasis of the lungs. The postnatal handling of these infants now includes (1) postural draining; (2) aspiration of the upper air passages with suction and a No. 10 catheter; (3) aspiration of the stomach with suction and a No. 10 catheter and (4) the placing of the infant in an oxygen incubator where it will remain for a period of five days. Dehydration is accomplished by the postponement

of parenteral or oral fluid for a period of forty-eight hours. A striking reduction in morbidity has followed these procedures.

The postpartum course of the mothers has usually been uncomplicated. Hypoglycemia has occurred infrequently only. Lactation has seldom been adequate. There have been four instances of thrombophlebitis, one of pelvic peritonitis and one of postpartum hemorrhage. The diabetic susceptibility to pyelonephritis has been evident in this group, but otherwise the postoperative, postdelivery course has been relatively uncomplicated.

A follow-up of the mothers shows that two (0.5 per cent) subsequently developed carcinoma. Case 13335 developed carcinoma of the breast and Case 27580 carcinoma of the esophagus. Neither of these patients had received hormonal therapy. Four of the patients subsequently died, three of cardiovascular disease and one of diabetic coma. A few have exhibited striking increase in tolerance for carbohydrate and no increase in severity of diabetes has been noted.

The follow-up of the infants has shown that clinical diabetes developed once. In this instance the child of two diabetics showed the classical signs and symptoms of diabetes at the age of six years. Another patient not in this series had a glucose tolerance test which deviates slightly from the normal. Except for the high incidence of congenital defects, most of which have been slight in character, and obesity noted most commonly at the age of six, the course of the infants has been normal.

Much that is controversial still exists in this problem of pregnancy complicating diabetes. That the clinical course in the obstetric diabetic patient is abnormal and that the fetal survival rate is significantly low are now two facts agreed upon by most students of the problem. In our experience in addition to sex hormonal imbalance, duration of diabetes and its coincidental vascular problems had an unfavorable effect upon the course and the fetal survival rate. Although the pre-diabetes or latent diabetes may have a harmful effect, it is

not comparable to that of long-standing diabetes. When diabetes had existed for more than twenty years, the fetal survival rate in patients receiving treatment for diabetes alone for the entire period has been only 20 per cent; and when vascular disease had progressed so far that the pelvic arteries were calcified and the treatment employed was that for diabetes alone, in our experience, the fetal survival was only 10 per cent.

The controversial points include an explanation of the mechanism, particularly which of the endocrine glands is primarily at fault, the placenta, the pituitary, the adrenal or all three. Abnormalities of placental sex hormonal balance have been demonstrated. Normal or elevated excretion of 17-ketosteroids, normal eosinophile count in treated cases suggest that in this group the function of the pituitary and the adrenal cortex at least in some respects are normal. With failure of sex hormonal balance, overfunction of the pituitary and subsequent overfunction of adrenal cortex is not an illogical theory.

Controversial, too, is the explanation of the size, the edema and the splanchnomegaly in the infant. Is it the response to pituitary, adrenal, cortical or chorionic gonadotropin, or perhaps to all three? Still more controversial is the concept of therapy. Is it stimulating or replacement? Clinical experience suggests the latter. Newer methods for assays of estrogen may in a short time solve this problem.

If we consider that the background favor-

ing normal pregnancy includes normal function and structure of the pituitary, ovaries, uterus, placenta, liver and enzyme system, it is little wonder that the clinical course in the diabetic is abnormal and the fetal survival low; for the kidney in the young diabetic has revealed a latent vascular disease, the enzyme system of the diabetic is under suspicion, the function of the liver can be altered by abnormal deposition of glycogen and fat, the uterus and ovaries are those of suspicion, the placenta has failed in its production of sex hormones and, without the inhibiting influence of estrogen and progesterone, pituitary overactivity may occur.

Thus diabetes through its disturbed metabolism, hormonal imbalance, the transmission of congenital defects and vascular disease does have a profound effect upon the course of pregnancy and the structure and behavior of the child. The disturbed metabolism and the hormonal imbalance are the correctible parts of our problem; and although the expected fetal survival in diabetes today is 90 per cent, only when the entire genetic and vascular problem of diabetes is solved will our experience be equal to the best in non-diabetic, obstetric and pediatric experience.

REFERENCE

1. GELLIS, S., WHITE, P. and PFEFFER, W. Gastric suction: a proposed additional technique for prevention of asphyxia in infants delivered by cesarean section. *New England J. Med.*, 240: 533, 1949.

Arteriosclerosis and Diabetes^{*}

JOSEPH H. BARACH, M.D.

Pittsburgh, Pennsylvania

THE relationship between diabetes and arteriosclerosis is a particularly intimate one. Arteriosclerosis, which can no longer be considered a disease exclusively of the second half of life, is being shown more and more to occur in the relatively young, particularly in diabetics. Additional data are needed, however, before we may say that severe or uncontrolled diabetes or ketosis leads directly to more extensive arteriosclerosis than would develop in mild or controlled forms of the disease.

Outstanding contributions toward the present day viewpoint have come from the observations of Dolger³³ who showed how few diabetics escape vascular lesions after fifteen or twenty years of the disease; of Dock¹⁴ and others who called attention to the relative frequency of coronary arteriosclerosis and infarction in the young; and of Priscilla White¹ and associates, who went "all the way" in showing the high incidence of vascular lesions in the young and in very young diabetics. We now seem justified in speaking of the universality of arteriosclerosis in diabetes.

The pathologist finds it convenient to divide arteriosclerosis into three types: (1) atherosclerosis, which is considered to be essentially a disease of the intima, (2) medial sclerosis, the Mönckeberg's type⁴² which in the main involves the media and (3) arteriolar sclerosis, which also includes intercapillary renal lesions. While all three are found both in the non-diabetic and in the diabetic, they occur much earlier and more extensively in diabetics. It is atherosclerosis with its intimal plaques that leads to coronary lesions and that in our day is of

utmost clinical importance. Studies of these plaques in both their early and advanced stages have thrown some light on the mechanisms at work in the pre-thrombotic states but much more is yet to be learned along these lines. The pathologist would like to be able to tell us whether the cholesterol deposits are primary or secondary and whether they are of endogenous or exogenous origin, but he does not have sufficient evidence to supply the final answers.

Medial calcification, in the main, consists of deposits of calcium in the media of muscular arteries, particularly in those of the lower extremities. While the changes which precede calcium deposits are not too well understood, we do know that they are more complex than simple deposition of fat. Of clinical importance is the fact that medial calcification does not narrow the lumen of a vessel. That is why a diabetic may have marked medial calcification which does not lead to vascular narrowing and subsequently to gangrene.

DISTRIBUTION OF ARTERIOSCLEROSIS IN ANIMALS AND MAN

Arteriosclerosis is largely a human disease but is also found in carnivora and herbivora. It occurs in mammals, lower vertebrates and birds, more so in some species than in others. It is not common in monkeys, cats and dogs but does occur not infrequently in cows, horses, marsupials, parrots and shore birds which show medial sclerosis and plaques. Arteriosclerosis is not uncommon in chickens and geese fed or overfed for market. Physically active animals show less,

^{*} From the University of Pittsburgh School of Medicine and the University Clinic, Pittsburgh Medical Center, Pittsburgh, Pa.

inactive birds like the goose and parrot show more arteriosclerosis.

Many and varied accounts have been written on the incidence of arteriosclerosis as well as hypertension in certain races and tribes of mankind the world over. Arteriosclerosis is notably absent among the poorer classes in Southern China, in certain regions in India particularly among vegetarians, in the Kenya Colony of Africa, in Puerto Rico and in the Eskimo. The Chinese referred to live largely on rice, with very little animal protein and animal fat. Arteriosclerosis is uncommon in Mohammedans who do not eat meat and in Puerto Rico where the diet is low in animal protein and fat. Necropsies in Okinawans by Steiner³¹ revealed sclerosis of the aorta in only 7 of 150 autopsies and complications and sequelae of arteriosclerosis were not seen at all. There were no cases of coronary occlusion. The diet of the Eskimo is not blubber as is commonly stated; actually he depends on the viscera and muscle of animals for his daily food. Kean and Hamill³⁹ in a recent report on the anthropathology of hypertension find that in certain African tribes blood pressure does not increase with advancing years as it does in this country and in Europeans. This was also true for groups of poor Chinese who live on sparse diets but not so true for the wealthier ones. Panamanians have little hypertension and they show no increasing pressure with advancing years. Zuni Indians have low arterial pressure. All of this is related more or less to the problem of arteriosclerosis.

ETIOLOGY OF ARTERIOSCLEROSIS

Here we would do well to consider the long and patient studies of Timothy Leary, who believes that atherosclerosis (and arteriosclerosis) is essentially a metabolic disease. Human beings have a limited capacity to destroy or excrete cholesterol, which accumulates in the blood and tissues just as uric acid does in the tophi of the joints and tendons of persons with gout. Cholesterol combines with fatty acids to form cholesterol esters. According to the concept of Leary,

atherosclerosis is due to production of crystalline cholesterol esters during periods of excessive ingestion of cholesterol in the following sequence: (1) cholesterol is esterified in the liver; (2) it is removed from the liver by Kupffer cells functioning as phagocytes, carrying the crystalline esters through the lungs into the systemic circulation, finally invading the arterial intima and (3) these crystalline esters, Leary contends, are just as irritating to the intima as silica is to lung tissue in silicosis. Leary contends that in this way deposit of fats leads to calcification, distortion of the artery and finally to the typical late effects and sequelae characteristic of arteriosclerosis.

Wilens considers nutritional factors of major importance in the etiology of atherosclerosis and arteriosclerosis. He notes that only too often lesions referred to as arteriosclerosis actually are of the atherosclerotic type. Included among the clinical consequences of these atheromatous lesions of the intima are angina pectoris, apoplexy and gangrene of the extremities, all of which are characterized by marked narrowing of the vascular channels. As a result of his studies Wilens is inclined to believe that such lesions might be prevented even though they cannot be healed or made to disappear. Wilens has observed histologic evidences of improvement or reversion of the lesions under certain conditions and believes that such lesions might even be brought under clinical control. During periods of marked loss in weight, says Wilens, the lipid content of intimal plaques may diminish or disappear. At necropsy he found that 67 per cent of persons without terminal weight loss had atherosclerosis while of those who had lost considerable weight only 38 per cent showed a comparable degree of atherosclerosis. Weight loss of only a few months' duration may be sufficient to cause reduction or withdrawal of lipids with a reversal of the atherosclerotic process. At the same time Wilens is not prepared to accept the dictum that this disease is altogether a disorder of nutrition, or to be more specific, a primary disorder of cholesterol metabolism.

Instead he proposes that the excess lipid material in the vessel wall might be of endogenous rather than of exogenous origin. Along with cholesterol, such lipids as phosphatides and neutral fats also are present in atheromatous lesions.

It has been realized for many years that infection is not an important factor in the etiology of arteriosclerosis and everything that is known bears out that viewpoint. It is known that during certain acute infections the blood cholesterol levels fall. During convalescence there is an up-and-down phase after which the formerly normal levels are re-established. Chronic infections, notably tuberculosis, are not productive of arteriosclerosis; in fact, the tuberculous subject is strikingly free of arteriosclerotic lesions at necropsy.

In so far as endocrine disturbances are concerned in their relationship to arteriosclerosis, not enough is known concerning the function of the individual endocrines, of their various combined effects, their action and their interactions. It is known that testosterone and estradiol inhibit hypercholesterolemia and atherosclerosis in rabbits. Pancreatectomy is followed by diabetes and diabetes is followed by arteriosclerosis. Radiation-induced or surgical thyroidectomy is followed by myxedema which in turn is followed by high cholesterol and atheromatosis. Thyrotoxicosis or thyroid extract in large doses reduces hypercholesterolemia and atheromatosis.

Age no longer is considered the dominant factor in arteriosclerosis. The decrescent period of life is the time when arteriosclerosis is most frequently noted but it is not duration of the life span which of itself is responsible. Arteriosclerosis occurs in time but it is not caused by time. The processes behind arteriosclerosis will in all probability be found to be biochemical and physical.

Sex has been considered an important factor in predisposition to arteriosclerosis. While it seems that in non-diabetics there is more peripheral vascular disease in males than in females, in diabetics the number of

cases of foot gangrene that we see is about the same in both sexes. Obesity is much more prevalent in the female. These facts, of course, serve to emphasize the importance of diabetes and obesity as related to arteriosclerosis.

Occupation has been considered significant in this connection; if this means anything at all, it is recognition of the fact that mechanical strain or injury, wherever and however it occurs, is added insult which quickens the cycle of pathologic events that follow. Wilens, as others before him, emphasizes the importance of intravascular pressure plus the element of gravity which comes with the vertical posture. Intimal plaques are found more commonly in arteries in which the blood pressure is higher because of the upright position of the body.

Inheritance is undoubtedly an important factor in arteriosclerosis. The importance of family history in diabetics with vascular disease needs no emphasis. It is our experience that the diabetic in whom we find advanced arteriosclerosis frequently gives a history of cardiovascular disease in his antecedents. He also presents other evidences of the diabetic "anlage." The diabetic with manifestations of impending gangrene in his misshapen, calloused and bunioned feet will almost invariably tell the doctor, if the doctor will enquire, that his or her father or mother had feet or toes just like his own. The experienced clinician has long realized the importance and frequency of the inheritance factor in hypertension, arteriosclerosis, coronary disease and peripheral vascular disease. The inheritance factor in xanthomatosis and hypercholesterolemia is likewise well known. Here the studies of Wilkinson⁴⁰ in essential familial hypercholesterolemia are of interest. Wilkinson records four generations including 350 individuals among whom 35 manifested the syndrome of high blood cholesterol, xanthoma tuberosum, valvular heart disease, angina pectoris and electrocardiographic changes. Comparable findings were recently reported by Boas, Parets and Adlersberg²⁷ in

122 cases of proved coronary atherosclerosis before the age of fifty.

Overnutrition and obesity, whether the result of excessive feeding or abnormal heat conservation or suboxidation, can be shown statistically to be conducive to arteriosclerosis. In the obese hypercholesterolemia is twice as common as in the non-obese. As Wilens said, a thin person of fifty has less sclerosis than a fat one at the age of forty. Hypercholesterolemia is a common finding in obesity, hypertension, lipoid nephrosis, myxedema and in uncontrolled diabetes. In our own experience when a diabetic in the hospital is brought under satisfactory control, in most if not all cases the blood cholesterol descends to a definitely lower level.

With regard to alcohol there is little experimental evidence that alcoholics have more or less arteriosclerosis than non-alcoholics. When cholesterol and alcohol were given together, the blood cholesterol level was higher but neither the liver nor aorta showed arteriosclerotic lesions (Wertheim).¹ There is little evidence that the solvent action of alcohol on cholesterol aids in its diffusion or local concentration. It was noted by Ruffner (1921) that Mohammedan pilgrims who abstain from alcohol are relatively free of arteriosclerosis. Chronic alcoholics, who obtain a large portion of their daily caloric requirement from alcohol and therefore live on a relatively low diet, are remarkably free of aortic atheromatosis and arteriosclerosis.

Nicotine is known to cause coronary spasm and nicotine poisoning is without doubt a harmful factor. There is the tobacco angina, angina of effort which can be induced by smoking and the reduction of tolerance to exercise when the patient smokes one minute following exercise. Certainly the mass of clinical evidence, in so far as coronary disease is concerned, overwhelmingly favors the idea that chronic nicotine poisoning is conducive to atherosclerosis, especially coronary disease.^{37,38} Occlusive vascular disease is definitely more prevalent in diabetics who smoke than in

non-smokers. Smoking usually reduces peripheral blood flow, increases pulse rate and blood pressure. In a few cases, especially in the elderly, these changes are less. This may be just as true whether the nicotine effect on the heart and vessels is direct or indirect.

EXPERIMENTAL PRODUCTION OF TYPICAL ATHEROMAS

In the dog experimental production of typical atheromas is accomplished by the administration of large doses of cholesterol by mouth, more so if at the same time thiouracil is given. In such animals cholesterolemia may reach 800 to 2,000 mg. per cent.¹ Tween 80 and Triton A20, synthetic detergents given to rabbits intravenously, cause a striking increase in blood cholesterol and phospholipid levels. Alloxan diabetes produces lipemia, cholesterolemia and atherosclerosis. On the other hand, others have reported that in cholesterol-fed rabbits alloxan diabetes tends to reduce atherosclerosis.

Interesting studies have been made by Steiner and co-workers who found that rabbits fed 1 Gm. cholesterol three times per week consistently show atheromatous lesions after forty days; if, however, choline in 0.5 Gm. doses is given simultaneously, atherosclerosis does not make its appearance up to the eightieth day. Doses of 1 Gm. of choline delay the lesions to 90 or 100 days. Feeding choline to old hens caused a reduction of cholesterol in the blood, aorta and liver.²⁰ Inositol and methionine, according to Hermann and others, reduce blood cholesterol levels; soya lecithin and thiocyanate also reduce blood cholesterol levels.²⁹

PROBLEMS FOR FUTURE RESEARCH

Numerous questions having more or less bearing on the etiology of arteriosclerosis await further clarification and answers. Among the basic questions are those relating to cholesterol and other lipids. What is the real significance of hypercholesterolemia? To what extent do restricted or semi-starvation diets influence hyperlipemia? Can an equilibrium be established between

ingested cholesterol or lipids, and cholesterol in the liver, brain, nervous system and the blood? Does the high incidence of arteriosclerosis in diabetes reflect a cholesterol imbalance in the diabetic? Pancreatic extract (lipoeaic)²⁹ has been said to exert delaying effects on atherosclerosis. Choline, inositol, methionine and soya lecithin have given favorable results in the restoration of normal cholesterol levels and possibly in the prevention of arteriosclerosis in experimental arteriosclerosis. Of what value are they in preventing, minimizing or abolishing atheromatous lesions? Is the cholesterol particle under certain conditions subject to physiochemical alterations which prepare it for an abnormal role and ultimately lead to deposition on the intima of the blood vessels. Moreton⁷ put forth the theory that the cumulative effect of many fatty meals over a lifetime, producing showers of large lipid particles in the plasma, is an underlying cause of atherosclerosis in humans. These large particles pass with the lymph into the intima, inciting local reaction. Triglycerides and fatty acids are resorbed but cholesterol remains.

It is known that cholesterol occurs in all animal cells but is present in greater amounts in fat tissues, in the brain and in the spinal cord. Fat is a solvent and the vehicle for cholesterol, and rabbits fed cholesterol in oil seem to develop arteriosclerosis earlier than those fed crystalline cholesterol. Cholesterol is taken in with fatty foods but can also be formed in the body from fats, protein and carbohydrate; any compound which an animal can convert to acetate can be utilized to make cholesterol. Cholesterol is the mother substance of adrenocortical substance and sex hormones. It is a universal constituent of tissues but it is not a universal dietary constituent. It exists in invisible combination in cells and in colloidal suspension in the blood. Under polarized light cholesterol becomes visible as solid crystals and crystalline esters.

Our knowledge of cholesterol synthesis and metabolism in the body is still frag-

mentary. Isotope technics introduced by Schoenheimer, Rittenberg and Bloch will doubtless throw additional light on the role of cholesterol metabolism in vascular disease. Feeding experiments with deuterium-labelled cholesterol, followed by examining the isotope content of the liver, aorta, coronary vessels and blood plasma, open the possibility of estimating both exogenous and endogenous cholesterol that will mark a definite step forward. By feeding heavy water it was shown that half of the cholesterol hydrogen atoms have their origin in body water and that any compound which the animal can convert into acetate can be utilized in the synthesis of cholesterol by the liver. Neutral fats can be labelled with iodine¹³¹ and plasma fat curves established for the normal and abnormal. Cholesterol tracers open up the possibility of studying the role of cholesterol from the time of ingestion to its deposit in organs and tissues, and to its final decomposition and rate of each of these steps.

Another problem pertains to the mechanical effect of increased intravascular pressure as it exists in established hypertension. The mechanical factor is illustrated when an artery comes into contact with a bony surface, such as the misplaced subclavian artery in the case of a cervical rib; such an artery is more apt to become sclerotic than one imbedded in soft tissues. Another instance is that in poliomyelitis; when one leg or arm is involved, the blood vessels on the flaccid side show less sclerosis than those with normal muscle tone. In Ayerza's disease it is the hypertension in the pulmonary circuit which is primary and the arteriosclerosis secondary. To what extent hydrostatic pressure effect is actually responsible for the lodgment and diffusion of lipid substance on and in the walls of blood vessels is not a settled question, although the concurrence of hypertension and arteriosclerosis is well known.

PROBLEMS AND PRINCIPLES OF TREATMENT

There are today new and interesting avenues of approach toward the possible

control of arteriosclerosis. Medical research, particularly in lower animals, indicates the possibility of arresting atherosclerotic processes and perhaps of reversion of processes already begun. We accept the fact that deposits of cholesterol in the intima of blood vessels occur in the early stages and the question is whether this occurs because of excessive amounts of cholesterol in the circulating blood or whether there is some alteration in the cholesterol molecule itself which under certain conditions initiates the lesion.

If excess cholesterol in the diabetic can be controlled or influenced favorably by the administration of insulin, will we do better from now on to use insulin more generously than we have in the past, at the same time avoiding hyperinsulinism? We have known for a long time that the large liver of young diabetics responds to generous doses of insulin. Does this imply that insulin improves liver function or fat metabolism or the restoration of a more normal enzyme and cholesterol metabolism, and ultimately may it delay or prevent arteriosclerosis?

Our approach to the treatment of arteriosclerosis, therefore, depends upon which viewpoints we accept as to its underlying causes and the relative importance of each. We can do nothing about the age of the patient but we may be able to do something about premature aging once we know how this depends on faulty nutrition. We can do little about hypertension until we know its origin and succeed in its control. We could do much, almost everything that might be necessary about diet control if only we knew just what should be done. If we admit that obesity is an underlying factor in atherosclerosis, and autopsy findings indicate that it occurs twice as frequently as in emaciated individuals, the necessary steps become clear to that extent. If the obesity is brought about by ingestion of excessive amounts of fatty foods, if the various fats and lipids act as vehicles for the diffusion of cholesterol throughout the circulatory system and if cholesterol, not readily metabolized, acts

as a foreign substance and an irritant and destructive agent to the vessel wall, our method of approach again becomes clear, namely, avoidance of overeating and subsequent obesity, a strictly low-fat and low-cholesterol intake by which we may eliminate two or three possible underlying causes—obesity, hypertension and hypercholesterolemia. Strangely enough, this concept takes us back to Anitshikow⁴⁴ in 1913, the very beginning of the still prevailing viewpoint in our day.

If on the other hand cholesterol deposits in the intima and subintimal layers are of endogenous origin, if the lipoids there are elaborated within the arterial walls, control of these processes must be found in the darker recesses of the human metabolism. That would inevitably lead us into the fields of endocrine functions and enzyme activities, into the physiology and pathologic physiology of liver function and into still other even less known fields. Even that, it may be, is not entirely hopeless; for if we may trust our other experiences, by restricting fat intake to a minimum we would still be reducing the fat that feeds the fires of atherosclerosis.

A basic question today is, whether fat is a final storage form of excess food which can only be burned and converted to carbon dioxide and water, or is it part of the metabolic pool of the body to which fragments are being constantly added and from which they are continuously being withdrawn for various uses?

However all these questions may finally be answered, we in our day must care for our patients in the light of present day knowledge. That calls for a sensible middle-of-the-road plan in keeping with the present and future probabilities of good treatment. Today, as far as I can see, our plan should aim at restoration and maintenance of a normal or ideal body weight; for this we have adequate standards.⁴¹ Our second aim is to allow our patients an adequate daily protein intake sufficient to prevent possible nitrogen deficit and hypoproteinemia, as may happen if we gave our patients less

than $\frac{2}{3}$ Gm. protein per Kg. body weight. Our next aim must be to give the patient the smallest amount of fat that will make up a satisfactory diet; one which the sensible patient will not refuse and one toward which he will cooperate with his doctor. For the diabetic this may nearly always be achieved with 75 to 90 Gm. of fat per day and there is also a choice in the kinds of fat. Today we are recommending the use of vegetable fats to a large extent, aiming thereby to reduce cholesterol intake. Until the time comes when it is proved that it is futile to recommend low-fat and low-cholesterol diets we will continue to advise against excessive use of eggs, milk, butter, lard, sweetbreads, fat meats, etc., all of them known to be rich in cholesterol and high in fat content. We advise the use of oleomargarine to replace butter, and vegetable oils to replace animal fats for cooking; skimmed milk or buttermilk as a beverage and minimal amounts of other fat foods. According to our figures the cholesterol content of everyday foods is about as follows: 1 egg contains about 0.3 Gm.; 3 ounces of meat contain about 0.3 Gm.; milk contains about 0.2 Gm. per quart; 3 ounces of liver contain about 0.3 Gm.; 3 ounces of smooth muscle contain about 0.2 Gm. cholesterol.

Needless to say, we have no recognized specific medication against athero- or arteriosclerosis. The use of choline, methionine, inositol, soya lecithin, etc., is still in the experimental stage and the results thus far reported in animals and man will require much more controlled observation to justify general clinical use.

REFERENCES

1. Seminar on Degenerative Lesions of Metabolism: Metabolism and Endocrinology Study Section. National Institute of Health, U.S. Public Health Service, October, 1947.
2. WILENS, SIGMUND. The relationship of chronic alcoholism to atherosclerosis. *J. A. M. A.*, 135: 1136, 1947.
3. KATZ, L. N. and DAUBER, D. V. The pathogenesis of atherosclerosis. *J. Mt. Sinai Hosp.*, 12: 382, 1945.
4. Proceedings American Society for the Study of Arteriosclerosis. *Am. Heart J.*, 35: 848, 1948; 36: 466, 1948.
5. HUBER, M. J., BROUN, G. O. and CASEY, A. E. Prevention of cholesterol arteriosclerosis in the rabbit by use of pancreatic extract (lipocain). *Proc. Soc. Exper. Biol. & Med.*, 37: 441-445, 1937.
6. BROUN, G. O., ANDREWS, K. R. and CORCORAN, P. J. V. Studies of the effect of lipotropic agents in experimental cholesterol atherosclerosis in the rabbit. *Am. Heart J.*, 35: 862, 1948.
7. MORETON, JOHN R. Physical state of lipids and foreign substance producing atherosclerosis. *Science*, 107: 371, 1948.
8. POLTZ, MILTON. Non-atheromatous lesions of the coronary arteries. *Am. J. M. Sc.*, 215: 91, 1948.
9. ANITSCHKOW, N. and CHALATOW, S. *Centralbl. f. allg. Path. u. path. Anat.*, 24: 1, 1913.
10. ASCHOFF, L. Lectures in Pathology. New York, 1924. P. B. Hoeber.
11. COWDRY, EDMUND V. Arteriosclerosis. New York, 1933. The Macmillan Company.
12. FRIDELL, DRUCKER and PICKETT. Histidine and ascorbic acid treatment of arteriosclerosis obliterans. *J. A. M. A.*, 138: 1036, 1948.
13. FRENCH, A. J. and DOCK, W. Fatal coronary arteriosclerosis in young soldiers. *J. A. M. A.*, 124: 1233, 1944.
14. DOCK, W. Atherosclerosis. *Bull. U.S. Army M. Dept.*, 4: 316-319, 1948.
15. HAYMANN, W. and RACK, F. Independence of serum cholesterol from exogenous cholesterol in infants and children. *Am. J. Dis. Child.*, 65: 235, 1943.
16. STEINER, A. Significance of cholesterol in coronary arteriosclerosis. *New York State J. Med.*, 48: 1814-1818, 1948.
17. HAYES, E. R. The present status of the relation of cholesterol to arteriosclerosis. *Minnesota Med.*, 31: 158-160, 1948.
18. MORRISON, LESTER M., HALL, LILLIAN and CHANEY, ALBERT L. Cholesterol metabolism: blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis. *Am. J. M. Sc.*, 216: 1916-32, 1948.
19. Combined Staff Clinics. Cholesterol metabolism and arteriosclerosis. *Am. J. Med.*, 6: 103, 1949.
20. HERMANN, G. R. Some experimental studies in hypercholesterolemic states. *Exper. Med. & Surg.*, 5: 149, 1947.
21. LEICHENGER, HARRY, EISENBERG, GEORGE and CARLSON, A. J. Margarine and growth of children. *J. A. M. A.*, 136: 388-389, 1948.
22. HORLICK, L. and KATZ, L. M. The effect of diethylstilbestrol on blood lipids and the development of atherosclerosis in chickens on a normal and low fat diet. *J. Lab. & Clin. Med.*, 33: 733, 1948.
23. PLOTZ, MILTON. Possible hazards of high fat diets in coronary disease. *J. A. M. A.*, 139: 10, 1949.
24. HELD, I. W. Hypertension due to arteriosclerosis and its complications. *M. Clin. North America*, 30: 659, 1946.
25. CHAMBER, WILLIAM N. Blood pressure studies in 100 cases of coronary occlusion with myocardial infarction. *Am. J. M. Sc.*, 210: 40, 1947.
26. WILENS, SIGMUND L. Orthostatic influence on the distribution of atheromatous lesions in the cerebral and other arteries. *Arch. Int. Med.*, 82: 431, 1948.
27. BOAS, ERNST P., PARETS, ALBERT and ADLERSBERG, DAVID. Hereditary disturbance of cholesterol

- metabolism: a factor in the genesis of arteriosclerosis. *Am. Heart J.*, 25: 611-22, 1948.
28. Editorial. Heredity in essential hypertension. *J. A. M. A.*, 136: 254, 1948.
 29. EILERT, MARY LOU and DRAGSTEDT, LESTER R. Lipotropic action of lipocaic; a study of the effect of oral and parenteral lipocaic and oral inositol on the dietary fatty liver of the white rat. *Am. J. Physiol.*, 147: 346, 1946.
 30. RABINOWITCH, I. M. Relationship between impairment of liver function and development of arteriosclerosis in diabetes mellitus. *Canad. M. J.*, 58: 547-56, 1948.
 31. STEINER, P. E. Necroses on Okinawans—anatomic and pathologic observations. *Arch. Path.*, 42: 359-380, 1946.
 32. WILENS, S. L. Bearing of general nutritional state on atherosclerosis. *Arch. Int. Med.*, 79: 129, 1947.
 33. MOTASHAW, MURZBAN D. Acute coronary occlusion. *Indian Physician*, 7: 11-17, 1948.
 34. GIVNER, ISADORE and LODYJENSKY, CATHERINE. Ocular findings in 120 juvenile diabetics. *New York State J. Med.*, 47: 1371-72, 1947.
 35. DOLGER, HENRY. Fundus oculi as an indicator of vascular damage in diabetes mellitus. *Arch. Ophth.*, 37: 695-97, 1947.
 36. MARDONES, R. J., JINENEZ, P., and MUSATADI, L. Influence of thyroid function on the protective action of potassium iodide in arteriosclerosis induced by a high cholesterol diet. *Rev. de med. y aliment.*, 6: 201, 1945.
 37. STEWART, H. J., HASKELL, H. S. and BROWN, H. The effect of smoking cigarettes on the peripheral blood flow in subjects in the older age group with coronary arteriosclerosis and hypertension. *Am. Heart J.*, 30: 541, 1945.
 38. WEINROTH, L. A. and HERZSTEIN, J. Relation of tobacco smoking in arteriosclerosis in diabetic patients. *J. A. M. A.*, 131: 205, 1946.
 39. KEAN and HAMMILL. Anthropology of arterial tension. *Arch. Int. Med.* 83: 535, 1949.
 40. WILKINSON, C. F., JR., HAND and FLIEGELMAN. Essential familial hypercholesterolemia. *Ann. Int. Med.*, 29: 671, 1948.
 41. BARACH, JOSEPH H. Normal standards in the treatment of 100 cases of diabetes mellitus with insulin. *J. A. M. A.*, 82: 347, 1924.
 42. SILBERT, SAMUEL and LIPPMANN, HEINZ, I. Moenckeburg's sclerosis: clinical entity. *J. Mt. Sinai Hosp.*, 12: 689-700, 1945.
 43. BARACH, JOSEPH H. Maximum Longevity Tables: Diabetes and Its Treatment. P. 246. London, 1949. Oxford Univ. Press.
 44. ANITSCHKOW, N. Experimental Arteriosclerosis in Animals. Arteriosclerosis. Edited by E. V. Cowdrey, Chap. 10. New York, 1950. Macmillan Company.

Management of Diabetes in a General Medical Practice

RUSSELL M. WILDER, JR., M.D.

Minneapolis, Minnesota

THE majority of patients with diabetes are and must of necessity be cared for by physicians who do not regard themselves as specialists in this field. It is with this group of physicians in mind that this article has been written, the purpose being to describe a practical and simplified program of diabetic management. The program avoids on the one hand excessively rigid control which may be time-consuming and costly, and on the other hand inadequate control which inevitably follows inattentiveness to the principles of satisfactory treatment. The treatment of diabetic emergencies, such as acidosis, is beyond the scope of this paper. I am concerned here primarily with the management of the diabetic patient who is ambulatory.

No time should be lost in establishing adequate control in any patient in whom more than minimal glycosuria has been demonstrated. Such a patient is to be considered a diabetic until or unless the glycosuria proves to be benign. The patient in whom glycosuria is more or less accidentally discovered as a result of an office examination is not infrequently highly reluctant to enter the hospital and to assume what he is apt to regard as an unnecessary and unwarranted expense. The patient must be told that satisfactory treatment is based on accurate diagnosis. Fasting blood sugar determinations and (in borderline cases) glucose tolerance tests may be needed. The well equipped hospital will have facilities for laboratory investigation, not all of them likely to be available in the physician's office. The need for highly accurate laboratory procedures should be

cited in urging hospital entry. There is a psychologic advantage in hospitalizing the diabetic patient shortly after his disease is discovered. If his physician regards his disease as serious enough to require hospital observation and instruction, the patient tends to be impressed by the potentially serious nature of his illness and is apt to receive his instruction in a more cooperative mood than might be attained in the physician's office. It is well for the patient to concentrate almost exclusively on the management of his diabetes during this introductory phase when a period of hospitalization will not seriously interfere for long with his usual work and activities. Getting him away from the well meaning but often ill advised sympathy of his friends and family is helpful. Finally, hospital instruction of the patient with the concentrated cooperation of the resident staff, nursing staff, dietetics department and the physician means an inestimable saving in time for both the patient and his doctor.

The patient is admitted to his room and instructed first in the collection of urine specimens for testing. A good routine involves testing a *freshly* voided urine specimen four times a day, before meals and at bedtime. The patient (and the nursing department) must thoroughly understand that a fresh specimen means urine which has been recently filtered through the glomeruli. The bladder must be emptied about half an hour before the test specimens are obtained in order that they may represent a fairly accurate index of the corresponding blood sugar values for the same time period, and contain a relatively small proportion, if any,

of "overflow glucose" spilled into the urine from a preceding meal. The nurses usually share the responsibility with the physician for teaching the patient to test his urine, using either qualitative Benedict's solution or the handier self-heating compressed testing tablets. Twenty-four hours after admission most patients test their own urine with only minimal supervision.

The diabetic patient deserves a painstakingly thorough physical examination with perhaps more than usual emphasis on the skin, mouth and odor of the breath (acetone); the height and weight; and examination of the ocular media and fundi. Not infrequently diabetes can be suspected from lens or retinal changes, and the physician who sees patients with diabetes will find his ophthalmoscope one of his most valuable aids. However, the physician's findings ought periodically to be checked against those of a competent ophthalmologist to be sure that development and progression of cataracts and diabetic retinopathy are not overlooked.

The size of the liver should be estimated by percussion and palpation. The status of the peripheral circulation especially in regard to presence or absence of pulsations in the arteries of the feet is of great importance. Evidence of diabetic neuropathy must be searched for. Reflex changes and absent or diminished vibration sensation in the lower extremities are particularly important as probable early manifestations of "diabetic neuritis."

Before breakfast on the morning after hospital admission blood is secured for determination of glucose and plasma cholesterol values, for hematologic examination, for a Wassermann test and sedimentation rate. A routine chest x-ray ought to be part of the initial examination. The need for other laboratory procedure such as the basal metabolic rate, other x-rays, such as those of the feet or pelvis for calcification of arteries, or of the stomach, gallbladder or colon, must be determined from the history and findings of the physical examination. If there is suspicion of chronic pancreatitis

a flat plate of the region of the pancreas for evidence of calcinosis of the pancreas should be obtained before the roentgenologic study of the stomach, gallbladder or colon.

The diabetic customarily starts his dietary program with regimen containing 1,200 to 1,800 calories, which is to serve only as a temporary diet until a formula can be tailored to fit his needs. If, however, the fasting blood sugar level is found to be normal so that the diagnosis of diabetes mellitus is questionable and a glucose tolerance test is decided upon, the patient must be given a general diet with a generous proportion of carbohydrate for at least two days before the test is made. It will be remembered that a normal individual who has been subjected to a diet restricted in carbohydrates for as short a period as twenty-four hours or who has been subjected to prolonged fasting may show a diabetic response to a glucose tolerance test.

A fairly common oversight in the instruction of the diabetic patient in the dietary management of his disease is the apparent assumption that a patient who is in a hospital bed and who is satisfactorily controlled on say 1,800 calories with a small dosage of protamine insulin will do equally well when he is out of bed and actively at work. The error is serious because the patient gets hungry when he is working, has to eat more to feel comfortable and then is either bothered by a guilty conscience when he next sees his physician or avoids his next appointment entirely. This mistake can easily be avoided by carefully going over the patient's usual activities with him and basing the prescription for the dismissal diet on his probable daily energy expenditure.

Using either the Boothby and Berkson nomogram or a convenient slide rule, a forty year old male patient whose ideal weight is 160 pounds and who is 5 feet, 10 inches in height will be found to need 1,740 calories as his basal requirement (rest in bed or chair). For sedentary work 30 per cent should be added to this figure and for moderately heavy work 40 to 50 per cent.

If he is moderately active, he will need 2,450 calories; while on a day that he plays several sets of strenuous tennis or eighteen holes of golf, his need will increase to 2,600 calories or more.

When a diet order is written after the patient's admission to the hospital, it is well to make sure that this is not interpreted by the patient or by the dietitian as a discharge program. In general the patient will need an increased caloric intake of approximately 20 per cent over his hospital diet when he goes home, unless a weight reduction program is in order.

One drawback to the hospital instruction of the otherwise ambulatory diabetic lies in the enforced inactivity commonly associated with institutionalization. This can largely be avoided, the patient's insulin requirement lowered and his status more closely brought to approximate that of his daily home life if, after the first twenty-four to forty-eight hours, he is urged to get out of the hospital several times each day to take some moderate form of exercise such as a brisk half hour walk. In this way an artificial situation can be produced which roughly mimics his average daily activity at home and gives the physician a more secure basis for judging both dietary and insulin requirements than can be determined otherwise from hospital observation alone.

Once the patient's diet prescriptions have been written, the details of dietary management, food substitutions and the weighing or measuring of food portions may be safely entrusted to the hospital dietitian. She should be able to secure the complete cooperation of that member of the household who will be responsible for planning and cooking the meals. However, even though the patient does not actually perform the meal planning or cooking, he should be carefully instructed in the fundamentals of his diet to take care of situations in which meals are eaten away from home or in which he has to prepare his own meals.

The patient whose diabetes is severe enough to require insulin for adequate

regulation is shown how to measure and regulate his dosage, and should be fully capable of continuing to administer his own insulin by the time he is ready to go home. Even those patients whose diabetes is adequately controlled by dietary restriction alone ought to have basic instruction in the administration of insulin to prepare them in case it should be needed at some future date. Such patients should have the experience of self-injection of a minimal and harmless dosage of 5 units or less of unmodified insulin taken just before a meal.

Approximately 50 per cent of one's diabetic patients will be capable of regulation without insulin. Another 25 to 30 per cent will require less than 30 units of insulin daily; this group is best handled on protamine insulin in one daily injection. The remaining group of diabetics, the so-called "Group iv," is apt to do poorly on protamine insulin alone. With dosages large enough to control day-time glycosuria night-time reactions are all too frequent. A smaller dosage of protamine-zinc insulin supplemented by unmodified insulin before each meal will give excellent control but leaves the patient with the unhappy prospect of giving himself three or four injections each day.

On the whole, this group of severer diabetics does best on a mixture of protamine and unmodified insulin taken one-half hour before the morning meal. The first day or two of diabetic regulation in the hospital will give valuable clues as to the probable magnitude of the patient's insulin needs so that by the second or third day one can switch to a mixed insulin dosage, changing the proportion and amounts of the two insulins depending upon the early morning and late afternoon urine tests. The principle of mixed insulin technics has been adequately and thoroughly discussed elsewhere.^{1,2} For the majority of these diabetics a mixture containing a ratio of regular to protamine insulin of 2:1 seems to be most satisfactory, although the mixed insulin technic is sufficiently flexible to be adapted to almost any type of insulin

requirement, such as 1:1, 1½:1, 2:1, 3:1, and even 4 and 5:1. The development of new insulin currently designated NPH-50 and now on clinical trial³ promises even simpler regulation for these severer diabetics. Many of the milder diabetics who do satisfactorily on a 2:1 insulin ratio (two parts of regular to one part of protamine insulin) also apparently are well controlled on globin insulin. I have used globin insulin satisfactorily in relatively few cases with excellent day-time control and reasonably good night-time control.

The patient using insulin must be carefully informed about insulin reactions: how to prevent them, how to recognize them and how to treat them. He must thoroughly understand that when the specimens of urine are continuously sugar-free for several days, the dose of insulin is to be reduced by at least 2 units. He must regard any unusual symptoms as possibly meaning the onset of a reaction, in particular any increased perspiration, any tremor or double vision. Finally, he must always carry sugar in some form on his person (loaf sugar is best) and must immediately take a loaf or two of sugar or the equivalent of this when symptoms of reaction—unusual perspiration with tremor and weakness—have developed.

The behavior of a person in a more severe reaction suggests inebriation; later coma supervenes. To avoid the embarrassment that this may occasion and to insure early treatment, every diabetic ought to carry on his person a card which gives the following information:

I have diabetes and my present condition may be owing to an overdose of insulin. Place sugar or candy in my mouth. If it fails to restore me in fifteen minutes, call my physician or send me to a hospital.

My name is _____

My physician is Dr. _____

His address is _____

His telephone number is _____

The patient has now learned about his diabetes and his dietary requirements, he

knows how to test his urine for sugar, he knows how to regulate and administer his insulin dosage, how to recognize insulin reactions and how to treat them. He has been in the hospital for a period varying from three days to a week and he is far better able to take care of himself than he was a few days previously. At this point he should realize that he is competent to manage his diabetes from 90 to 95 per cent of the time, barring the development of complications.

On his discharge from the hospital the patient should be instructed to test his urine before breakfast and before supper every single day. He is told to report to the physician for an office visit three to seven days later. This is partly to tie up any loose ends and to make sure that his instruction has been adequate and is thoroughly comprehended. Overlooked points will frequently turn up. At this visit the patient has the opportunity to go over his insulin dosage (if he is taking any) with the physician and to receive the assurance that he is administering the proper quantities of insulin if this is the case. The diet also is reviewed. If no serious difficulties are encountered, he can be discharged after this first office visit for a period of approximately three months with instructions to call the physician in the intervening period of time should any difficulties arise. When next seen, he is weighed, remeasured and his diet and insulin dosage evaluated in the light of his progress since leaving the hospital. In case he is getting too much or too little to eat, the services of the hospital dietitian may again be enlisted to help in working out a corrected dietary schedule.

If control is satisfactory the patient is given an appointment to return to the physician's office in approximately six months for a blood sugar determination. From then on he ought to be seen about twice yearly for help, encouragement, re-examination and instruction. If he is doing well, he ought to be told about it. If he is making mistakes, they should be corrected. Above all he should be continually en-

couraged to test his urine at least once a day, and if he is taking insulin, twice daily. The patient's carefully kept reports of his own urine tests are the most valuable contribution which he can make to his physician; they give far more information as to the progress of diabetic control than any number of blood sugar value determinations could do. Blood sugar determinations have been overworked and given an emphasis out of all proportion to their actual importance. They are expensive and often provide no information not already available from the results of simple qualitative urine sugar analyses. However, experience shows that the blood sugar determination serves as an inducement to maintain the continued interest of the patient in the proper management of his disease, and for this reason alone it should be made at intervals not less infrequent than once every three to six months. Furthermore, it has the function, not served by urinalyses, of detecting hypoglycemia, and not infrequently a patient overenthusiastic about keeping all his urine specimens completely sugar-free will increase his dosages of insulin above what is required, thereby inviting insulin reactions.

There are two extremes of mismanagement of the patient with diabetes. The first is the overcontrol method in which the patient is given a diet, a prescription for insulin and appointments to return to the doctor at much too frequent intervals for urine sugar or blood sugar determinations, until he soon becomes almost completely dependent on the physician for the entire management of his disease. The other is the undercontrol method in which the patient receives dietary and insulin instructions, starts out by carefully testing his urine and even counting calories, but because of the physician's lack of interest and his own understandable desire to lead as normal a

life as possible and to think about his diabetes as little as possible, stops testing his urine for weeks and even months at a time, eats carelessly and takes insulin depending upon how he "feels." Sooner or later he becomes the patient whose only contact with the physician is during an illness, when he has a severe insulin reaction or when he is in acidosis. The wise physician will endeavor to set a course which carefully misses these extremes and will do his best to see that his patient avoids both overdependence and complete independence.

SUMMARY

1. A simplified method for managing the majority of diabetics seen in a general medical practice is outlined.
2. The importance of initial hospitalization for diagnosis, treatment and instruction is stressed. The few days spent in the hospital early in the course of the disease will mean an inestimable saving of time for both the patient and his physician.
3. The importance of daily or twice daily examinations for sugar of freshly voided urine specimens as indices of corresponding blood sugar values is re-emphasized.
4. Dietary instruction and insulin regulation are briefly discussed.
5. Follow-up management of the diabetic after his hospital discharge is described, and a plea is made for a program which avoids the extremes of excessively rigid control and of undercontrol.

REFERENCES

1. SPRAGUE, R. G. and UNDERDAHL, L. A. The use of insulin mixtures. *Minnesota Med.*, 30: 153-156, 1947.
2. WILDER, R. M. A Primer for Diabetic Patients. 8th ed. Philadelphia and London, 1946. W. B. Saunders Co.
3. KIRKPATRICK, N. R. Experience with a new insulin. *Proc. Staff Meet., Mayo Clin.*, 24: 365-370, 1949.

Diabetic Coma*

Metabolic Derangements and Principles for Corrective Therapy

GEORGE M. GUEST, M.D.

Cincinnati, Ohio

AMONG various complications of diabetes mellitus ketonemic acidosis and coma carry the most serious threat to the health and survival of the diabetic. The immediate hazards are evident; there is also increasing evidence that the late complications of degenerative cardiovascular disease are greatest among patients who have suffered numerous episodes of acidosis and coma.¹ Theoretically, such states should never develop in patients who are constantly alert in the observance of the few precautionary measures that are most essential. But when unexpected emergencies occur, the treatment of severe diabetic coma involves some of the most interesting and challenging problems in clinical medicine. Progressive stages in the development of diabetic coma are determined by a long series of closely interrelated functional derangements and chemical disturbances in the body, with secondary results that quickly become far more serious than the initial derangements of carbohydrate metabolism denoted by the name of the disease.

Like many other phases of diabetic management the treatment of coma has involved numerous conflicts of opinion among highly qualified authorities, sometimes leading to sharp exchanges of contradictions and reciprocal denunciations of various theories and practices followed in different centers. When closely examined some features of these conflicting views appear to be based upon argumentative distinctions without real differences in the

fundamental concepts to which nearly all subscribe; attention is often confined to one or two or three points out of many known to be important in the chemical pathology of coma; and explanations of success or failure of treatment sometimes have been oversimplified by emphasis on the use and abuse of single items in the therapeutic armamentarium.

FUNCTIONAL DERANGEMENTS

In the development of diabetic acidosis and coma numerous factors are involved in a vicious circle of events in which all appear to aggravate the respective courses of separate but closely interrelated metabolic disturbances: (1) *Insulin insufficiency* or ineffectiveness; (2) *impaired glycogenesis*, increased glycogenolysis, hyperglycemia glycosuria, diuresis; (3) *increased hepatic ketogenesis*, ketonemia, ketonuria; (4) *metabolic acidosis*, with decreased bicarbonate and pH of the body fluids, and with hyperpnea a principal physical manifestation; (5) *increased cellular catabolism* liberating inorganic phosphates, potassium nitrogen and other metabolites from intracellular organic compounds; (6) *losses of electrolytes* by increased urinary excretion; decreased concentrations of electrolytes in extracellular and intracellular spaces; (7) *dehydration*, occurring primarily from losses of electrolytes, aggravated by loss of water through glucosediuresis and by insensible loss of water through the lungs with the development of severe hyperpnea; hemoconcentration, diminished blood volume, falling blood pres-

* From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio. Aided by a grant from the Nutrition Foundation, Inc., New York, N. Y.

sure, shock, anuria; (8) *tissue damage*, resulting from increased cellular catabolism, anoxia and from release of "toxic" agents; (9) *coma*, resulting from ketonemic narcosis, cerebral anoxia, acidosis, etc.

These various factors are dealt with briefly in the following paragraphs as a basis for the subsequent discussion of treatment.

1. States of insulin deficiency may be defined as resulting from a lack of insulin, either endogenous or exogenous, or from circumstances leading to neutralization of the effects of available insulin. Ineffectiveness of insulin may result from the action of hormonal antagonists, specific antibodies, toxins or enzymes that destroy insulin, or of chemical conditions of the body fluids that inhibit enzymatic processes in which insulin is involved. It is obvious that many factors beyond a mere lack of insulin are operative in patients who require very large doses, sometimes huge, of exogenous insulin for the prevention of ketonemic acidosis or in the treatment of coma. Suggested causes of insulin resistance have been well reviewed elsewhere^{2,3} and need not be considered here. Suffice it to say that the development of ketonemic acidosis is always initiated by insulin-insufficiency, regardless of the mechanism responsible for an increased need. In cases with treatment well established the occurrence of coma is usually clearly traceable to omission of the usual daily dose of insulin, to injudiciously decreased dosage or to failure to increase the usual daily dosage as needed during infections or illnesses that lead to increased insulin requirements.

2. Hyperglycemia may be regarded as incidental to disturbances in the hepatic regulation of blood sugar levels,⁴ the result of decreased glycogenesis and increased glycogenolysis rather than a predominant disturbance of the ability of the tissues to burn sugar.⁵ Hepatic glycogen probably represents only a small fraction of the total carbohydrate utilized in the body through various metabolic channels. Low concentrations of glycogen in the liver may be due to lack of or ineffectiveness of insulin to

promote glycogenesis, to glycogenolytic effects of the adrenal, thyroid or pituitary hormones, to bacterial or viral toxins affecting the physical integrity of the liver cells and to starvation. Especially in children the element of starvation may be important in the depletion of glycogen reserves when there is failure of appetite, refusal of food or vomiting at the onset of infections. Varying degrees of hyperglycemia are not closely correlated with other severity indices of coma. Blood sugar levels may be very high in early stages of the development of a diabetic crisis and may fall considerably during coma (without insulin) presumably due to the exhaustion of carbohydrate stores in the whole body.

Hyperglycemia and glycosuria are concomitant factors leading to diuresis but *per se* are not critical in the chemical pathology of coma. Even extreme degrees of hyperglycemia in the absence of ketosis do not immediately lead to notable illness or functional disturbance other than diuresis although the latter may become intolerable to the patient.⁶ Excessive excretion of electrolytes accompanies diuresis in diabetic acidosis; but glucose-diuresis of itself does not necessarily lead to salt deficits except under conditions of insulin-insufficiency. In studies on osmotic diuresis Rapoport and co-workers⁷ recently demonstrated that when urine flow was greatly increased by loading with glucose (in non-acidotic diabetic patients receiving insulin), the excretion of Na and Cl tended to rise proportionately while that of K and P tended to remain constant. On the other hand, when an insufficient supply of insulin leads to increased cellular catabolism and release of intracellular components, an excessive loss of both intra- and extracellular electrolytes in the urine may be expected, regardless of the degree of diuresis.

3. Abnormally rapid hepatic ketogenesis is associated with increased glycogenolysis and decreased concentrations of glycogen in the liver. Mutually aggravating factors are operative, inasmuch as glycogenolysis is increased by the state of ketonemic acido-

sis. The theory of overproduction of ketone bodies in diabetic acidosis is now well accepted, with the establishment of evidence that the usual rate of utilization of ketones by muscles and other extrahepatic tissues is unimpaired in depancreatized animals.⁵⁻¹⁰ Ketonemia increases rapidly when overproduction exceeds both the capacity of the kidneys for secretion and the rate of utilization of the ketone bodies by muscles and other peripheral tissues.¹¹

4. Metabolic acidosis, characterized by low bicarbonate and low pH of the blood plasma, results partly from the accumulation of ketones and other acid metabolites, partly from losses of mineral cations that are excreted with ketone acids, phosphates and other anions in the urine; also, relative hyperchloremia often co-exists with a lowered concentration of sodium in the plasma, especially in later stages of increasing hemoconcentration. The state of acidosis *per se* aggravates the course of the metabolic disturbances by multiple effects, directly or indirectly interfering with the action of insulin and generally accelerating catabolic processes in all tissues; e.g., lowered pH of the fluids inhibits synthesis and accelerates the decomposition of intracellular phosphorylated compounds that are involved in the carbohydrate cycle. The hyperpnea that accompanies acidosis involves severe muscular effort, imposing burdens of fatigue and anxiety, and contributes to the development of dehydration, especially in late stages, by increasing the loss of water vapor in expired air. Correlating hyperpnea in acidotic patients with changes in blood pH, Kety et al.¹² observed respirations increasing sharply below a threshold at around pH 7.2 to a maximum in the region of pH 7.0 but decreasing with lower values as the severity of acidosis increased, probably owing to depression of the medullary centers.

5. Increased tissue catabolism in the diabetic crisis involves the liberation of inorganic phosphates and associated cations (especially potassium) from cells into the plasma whence they are excreted in the

urine unless renal function is impaired. Metabolic balance studies have furnished abundant data on the nature of the metabolic losses that occur in diabetic acidosis. Von Noorden in 1905 stressed the importance of phosphaturia in diabetic coma as an index of cellular catabolism. The classic study by Atchley, Loeb et al.¹³ demonstrated that losses of K and P were higher in proportion to N than the ratio found in tissues, indicating that labile intracellular compounds were lost without necessarily a complete cellular breakdown.

Insulin deprivation leads to an increase in basal metabolic rate and to increased glycogenolysis before acidosis is apparent. With the development of acidosis the low pH of the body fluids favors the enzymatic decomposition of labile organic phosphates in the cells. When the rate of breakdown exceeds the rate of phosphorylation and resynthesis of compounds involved in the glycolytic cycle, inorganic phosphates are liberated into the blood. Increased phosphaturia in states of acidosis has been commonly explained as a renal mechanism for conserving cations, for maintaining the alkali reserve in the plasma, diminished tubular reabsorption of phosphates occurring as an effect of lowered pH on the kidney.¹⁴ Increased liberation of inorganic phosphates from tissues is probably primary and the more important factor in phosphaturia.

6 and 7. Dehydration in diabetic acidosis results primarily from loss of electrolytes as it does in other conditions in which salt depletion leads to diminished ability of the body to retain water. Data from metabolic studies indicate that the losses are primarily cellular, depletion of extracellular elements occurring as a concomitant or secondary effect. In later stages vomiting (or the accumulation of fluid in a dilated stomach without actual vomiting) may aggravate the loss of extracellular electrolytes, chloride and sodium. The progressive manifestations of dehydration with depletion of total body fluids, hemoconcentration, diminished circulating blood volume, lowered blood

pressure and shock, are well known and need not be discussed here. The time element is important in determining the course of the depletion of the body fluids. When the evolution of acidosis and coma is rapid, dehydration may be less pronounced than when acidosis exists several days before the onset of coma and there is time for a greater total loss of electrolytes. Hypoelectrolytemia is found during the development of acidosis while polyuria and polydipsia are concomitant symptoms but the picture may change considerably in later stages when polydipsia ceases with loss of consciousness or vomiting interrupts the intake of water. At this time, rising levels of non-protein nitrogen may indicate inadequate renal function due mainly to a lack of water. In the stages of coma when hyperventilation is increasing and fever accelerates the rate of water loss by vaporization, the loss of water alone from the lungs in expired air and through the skin in insensible perspiration becomes an increasingly important factor aggravating the state of dehydration. Such water loss leads to hemoconcentration in the true sense, with increasing osmolarity of the plasma. This sequence of events is similar to that leading to plasma hyperosmolarity and hyperelectrolytemia in infants with gastrointestinal disease complicated by hyperventilation.¹⁵ Diarrheal disease ordinarily leads to dehydration from salt loss, characterized by hypoelectrolytemia, but with severe hyperventilation provoked by co-existent respiratory tract infection the picture may change rapidly to one of hemoconcentration from water loss, with extreme degrees of hyperelectrolytemia and hyperosmolarity of the blood plasma. Similar conditions may be found occasionally in diabetic coma. For example, in an infant, three months of age, suffering a respiratory tract infection and fever, with severe hyperpnea, probably acidotic more than forty-eight hours before the diagnosis of diabetes was made and treatment was started, the concentrations of total base and of Cl in the blood serum were 180 and 135 m.Eq./L., respectively.

8. A concept of irreversible tissue damage is generally offered to explain the high mortality that is universally found among comatose patients, rising sharply with the duration of coma regardless of treatment.¹⁶⁻²⁰ It is generally agreed that chemical analyses of the blood of patients before the start of treatment show little difference between those who recover from coma of short duration and those who have been comatose a long time who do not recover. Investigators have turned their attention increasingly to the cells, rather than extracellular fluids, seeking explanations for the damage that is associated with various indices of severity of coma. Damage to vital organs may be ascribed to factors of increased catabolism induced by acidosis, involving the liberation of phosphates and mineral ions as already mentioned, to specific histotoxic effects of ketone bodies, especially acetoacetic acid, and to interference with oxygen exchanges leading to tissue anoxia. The last item now appears to be the most important. In studies done on fourteen patients in severe coma, with mortality 43 per cent, Kety and co-workers¹² found that the measurement of cerebral oxygen consumption was the only one of many tests performed before or at the start of treatment that seemed to have prognostic significance. They report that in these patients "there seemed to be a critical level for cerebral oxygen utilization of 2.1 cc. per 100 Gm. of brain per minute at or below which consciousness disappeared, compared with a consumption of 3.3 cc. per 100 Gm. per minute found in mentally alert normal subjects." With but one exception a cerebral oxygen consumption below that critical level appeared to be incompatible with survival.

Acute functional disturbances of the heart and kidneys may be ascribed similarly to the effects of acidosis and of cellular anoxia attending a diminution in circulating blood volume, hemoconcentration and shock. In older persons there are usually the complications of already existent cardiovascular disease. Specific effects of changes in the

concentration of potassium in the blood plasma on myocardial function, in severe coma and in the postacidotic period have been revealed by electrocardiographic studies.²¹

9. Coma, the ultimate and most critical manifestation of the diabetic crisis, is the most important of clinical indices correlated with prognosis. In their extensive study of blood gases, electrolytes and cerebral blood flow in diabetic subjects, mentioned above, Kety and co-workers found a close correlation between mental states (normal, alert, confused, unconscious) and the rate of utilization of oxygen by the brain; also, there was a good correlation between mental state, depression of cerebral metabolism and rising levels of blood ketones. Coma was associated with a 40 per cent reduction in cerebral utilization of oxygen in spite of an augmented rate of cerebral blood flow and normal arterial oxygen saturation. Kety et al. concluded that the observed depression in cerebral metabolism could be ascribed both to the state of acidosis *per se* and to ketone substances probably acting as histotoxic agents.

RECOVERY

The steps involved in recovery from diabetic coma may be described as a reversal of those that characterize the development of acidosis. Again, numerous factors of metabolic adjustments are closely interrelated and mutually dependent upon the effects of various therapeutic measures: the administration of insulin and parenteral fluids, and realimentation.

Effective doses of insulin promote glycogenesis, inhibit glycogenolysis and hepatic ketogenesis and reduce tissue catabolism. The action of insulin is dependent upon available supplies of substrates for enzymatic reactions, e.g., sugar, phosphorus and potassium, and upon the influence of pH on the enzymatic transformations; perhaps also upon amounts of enzymes and coenzymes in the tissues. Insulin may promote processes of phosphorylation in extrahepatic tissues in ways not yet well understood, not entirely

linked with its blood-sugar-lowering effects or the transfer of sugar from plasma to cells.^{22,23a,b} Ketone bodies are eliminated partly by renal excretion, more by utilization in extrahepatic tissues.^{7,11} The replacement of ketone anions by bicarbonate is accompanied by restoration of normal pH values and by simultaneous shifts in the distribution of Cl, Na and other elements in extracellular and intracellular fluids. Parenteral fluid therapy is directed to the restoration of a normal circulating blood volume, replacement of electrolyte losses and rehydration of the whole body, essential to all phases of functional recovery. Processes of glycogen formation and re-establishment of normal carbohydrate metabolism in tissue cells involve the uptake of phosphorus and potassium from extracellular fluids. Concomitantly with recovery from acidosis, with rise of plasma pH to normal, the excessive urinary excretion of phosphate, potassium and other waste metabolites is sharply reduced; phosphaturia may be practically nil for several days after symptomatic recovery. The diminished phosphaturia is explained as the result of (1) changes in tubular reabsorption of P found with changes of pH in the blood, (2) diminished liberation of inorganic phosphates from cells as tissue catabolism is reduced and (3) lowered concentrations of inorganic P in the plasma. Metabolic equilibrium is reached *after* a normal nutritional state is restored by realimentation.

BLOOD CHEMISTRY

At each stage of development of acidosis and recovery the chemical state of the blood is the resultant of all processes that influence its changes. The composition of the plasma for the most part does not give an accurate indication of cellular changes. The direction and rate of chemical changes in the plasma, if determined by serial measurements at short intervals, would offer better indices of the physiologic state of the whole body than any static representation of the composition of plasma, e.g., as in diagrams depicting electrolyte structure of the plasma

at a given moment. Just as blood sugar levels depend upon rates of glycogenesis, glycogenolysis, gluconeogenesis, utilization and excretion of glucose, so the concentrations of inorganic P and K in the blood plasma depend upon the rate and direction of exchanges of these elements between the cells and plasma, and the rates of their excretion in the urine. The levels of inorganic P, K and non-protein nitrogen in the plasma usually remain normal or low during the early stages of the development of acidosis when urinary excretion of these elements is steadily increasing but their levels rise rapidly in later stages as the result of increasing cellular catabolism plus failure of renal function to "clear" the plasma. In severe coma concentrations of inorganic P and K in the plasma may be and usually are high despite an increasing deficit of these elements in the blood and other tissue cells.* With increasing acidosis Cl and Na ions enter the cellular phase as P and K leave the cells. The ratio of cellular chloride to serum chloride, a function of pH, offers an index of shifts in the distribution of Cl between cells and extracellular fluids in the whole body. It is to be noted that this ratio is relatively high in acidosis regardless of whether the concentration of Cl in the plasma be low or high. Some investigators have found elevated concentrations of pyruvic acid in the blood plasma a sign of cellular disturbances in which the coenzyme carboxylase (thiamine pyrophosphate), required for the metabolism of pyruvic acid through the Krebs cycle, may be inactivated or lost with other phosphorylated compounds.^{24a} During recovery when resynthesis of intracellular compounds involves a rapid uptake of P and K from the plasma, hypophosphatemia and hypopotassemia (with reference to plasma) indicate something of the rate and direction of exchanges occurring between cells and plasma, not the degree of deficiency of those elements in the body at a given time.

* As commonly used, the words hyperphosphatemia and hyperpotassemia apply only to plasma concentrations.

The organic acid-soluble phosphorus compounds of the blood cells constitute a labile store of phosphorus serving diverse functions in the body.²⁵ In constant state of flux, synthesized and decomposed through reactions of the glycolytic enzyme system, the phosphoric esters act as transport substances, participating in carbohydrate metabolism and in the transfer of phosphorus for various metabolic purposes; and as intracellular anions they play an important role in the ionic equilibrium of the blood. Although the total amount of phosphorus thus carried in the cells of the blood is small compared with the total labile stores of phosphorus in the body, the changes found in the red cells in different pathologic conditions offer a valuable index of the *state* of the stores of related labile compounds in other tissues. In diabetic coma there is always a profound reduction in concentration of the phosphoric esters in the red blood cells. During the development of and recovery from the acidotic state the direction and rate of changes in the organic phosphates in the blood cells give clues to the probable sequence of closely related chemical changes taking place in other tissues which are less easily studied than the blood.

The total organic acid-soluble phosphorus (OASP) of the red cells, normally around 50 to 60 mg. per 100 cc. of packed cells, is made up of approximately 10 mg. adenosinetriphosphate, 15 mg. hexosephosphates and 25 to 35 mg. diphosphoglycerate. These phosphoric esters normally constitute a considerable part of the intracellular anions. Expressed in milliequivalents per liter of water, in packed cells, the total average concentration of anions, 175 m.Eq., is comprised of HCO₃ 17, Cl 74, inorganic phosphate 1, organic phosphates 45 (of which the diphosphoglycerate represents about 30 m.Eq.), hemoglobin 33, and undetermined anion equivalents 5 m.Eq., estimated by difference. These anions are matched by the cations Na 22, K 144 and Mg 8 m.Eq. per L. of water. The phosphoric esters and hemoglobin together thus comprise about 78 m.Eq. of non-diffusible

anions, which influence the distribution of diffusible ions (Cl and HCO_3) between the cells and plasma according to principles of the Donnan equilibrium.²⁶ In various conditions in which large changes in concentration of Cl in the blood occur, a reciprocal relationship has been observed between the concentrations of organic phosphates and of chloride in the cells comparable to that found between Cl and HCO_3 in the plasma: e.g., high cellular chloride with low concentrations of organic phosphates in ammonium chloride acidosis and in diabetic acidosis and, conversely, low cellular chloride with high concentrations of organic phosphates following pyloric obstruction, and in nephritis with hyperphosphatemia.²⁷

All changes in concentration of the phosphoric esters necessarily hinge upon the enzymatic reactions of phosphorylation and dephosphorylation in the glycolytic cycle. Inorganic P enters this cycle in the phosphorylation of adenylic acid, with the formation of adenosinetriphosphate (ATP), and leaves the cycle when liberated from ATP after various intermediate steps of transferal in the formation and decomposition of hexosephosphate, diphosphoglycerate and other intermediate compounds. Principal factors influencing these transformations are changes in pH and in amounts of substrates available. By experiments *in vitro* it has been shown that pH values of 7.4 and above favor synthesis while values below 7.3 favor decomposition of the phosphoric esters and liberation of inorganic P from the cells.²⁸ Presumably the same effects of changes in pH are operative in conditions of severe diabetic acidosis and recovery: lowered pH leading to decomposition of intracellular organic phosphates and to excessive phosphaturia as long as renal function is adequate to clear the plasma of liberated inorganic phosphates; and normal pH values (after correction of acidosis) favoring the restoration of the organic phosphates.

Following the withdrawal of insulin in diabetic subjects who are prone to develop cells easily the concentration of phos-

phoric esters in the blood cells decreases rapidly with the development of keto-acidosis. If the duration of acidosis has been brief, resumption of insulin injections is followed by prompt restoration of the organic phosphates within a few hours, with correction of the state of acidosis and elimination of ketosis. The time relationships of such changes parallel closely those of the urinary losses of phosphorus and potassium that have been demonstrated during the development of acidosis and the retentions of P and K during recovery (Atchley, Loeb et al.¹³; Butler et al.²⁹ and others). That the state of acidosis *per se* is responsible for these changes is indicated by the fact that a similar sequence of changes may be observed in ammonium chloride acidosis: extreme phosphaturia accompanying a great decrease in concentration of organic phosphates in the blood cells during periods of administration of NH_4Cl ; cessation of phosphaturia and recovery of normal concentration of OASP in the blood cells when the NH_4Cl is stopped.²⁷ When phosphate losses have been large with prolonged acidosis in cases of severe coma, the restoration of organic phosphates in the blood cells is slow during recovery, lagging considerably (even for several days) behind the correction of ionic equilibrium in the plasma and clinical signs of recovery.^{30,31}

The transfer of mineral cations between cells and plasma is closely linked with the enzymatic reactions of phosphorylation. Changes in the concentration of organic phosphates and of K in the blood cells during the development of and recovery from diabetic acidosis are closely parallel, probably dependent upon common factors: low cellular concentrations of organic phosphates and K resulting from decomposition of the phosphoric esters in the acidotic state and from lack of substrate (either P or K or both) for their resynthesis in the recovery period.

The observations made on changes in the distribution of phosphorus compound in the plasma and cells of the blood, correlated with data from metabolic balance studies

afford a basis for the concept of two phases of altered mineral metabolism during the development of and recovery from diabetic acidosis: a phase of acidosis and dehydration, during which losses of both extracellular and intracellular ions and fluids occur; and a post-acidotic phase during which, with restoration of anabolic cellular functions, the avid uptake of intracellular ions by tissue cells results in a depletion of these ions in the extracellular fluids. Subnormal levels of inorganic P and K in the plasma in the recovery period may be ascribed to this uptake by the cells rather than to urinary excretion at that time as some have suggested.

Hypophosphatemia, characteristic of the recovery period, is not attended with recognized functional disturbances, but severe depletion of serum potassium results in the now familiar syndrome of hypokalemia, as described by Holler³² and others:^{33,34} generalized muscular weakness, paralysis of respiratory muscles and cardiovascular difficulties attended with characteristic changes in the electrocardiogram. Hypophosphatemia and hypokalemia are but two features of a series of postacidotic metabolic readjustments which may also involve Ca and Mg.³⁵ Under other conditions and in subjects with different nutritional backgrounds postacidotic readjustments may lead to manifestations of other deficiencies: e.g., tetany as a manifestation of hypocalcemia in the postacidotic period after diarrheal disease in infants.³⁶

THERAPY

In debates over various schemes for the treatment of coma many writers have rightly expressed fears of the harm that can be done by abuses of practically all of the commonly employed procedures. Examples have been cited of deaths that followed the administration of excessive amounts of glucose solution, alkali, salt solutions and even of insulin. Usually these reports lack clear evidence that deaths were in fact due to the procedure indicted and they do not constitute valid

arguments against a more judicious use of any of these valuable procedures. In many instances it could be claimed that the deaths were due to neglect of supportive therapy rather than to the specific abuses: e.g., failure to correct rapidly increasing acidosis by judicious administration of alkali; use of hypertonic glucose solution alone in large amounts without adequate salt replacement; use of large doses of sodium bicarbonate without adequate treatment with other fluids. Some deaths in the postacidotic period have been due to hypokalemia, a phenomenon only recently appreciated.

Primary objectives in the treatment of coma should be the restoration in the body of *optimal conditions for functional recovery*, as well as the supply of materials needed for the restoration of normal chemical structure of the tissues and fluids. Rules for the treatment of coma, to be helpful, must be flexible, permitting changes of procedure in individual cases according to the dictates of clinical judgment in evaluating the state of each patient, the severity and duration of acidosis, coma, hyperpnea and dehydration, evidences of recent loss of weight, the state of the blood-circulation and the presence of infection. Therapeutic procedures should be employed with attention to interrelationships existing among their separate effects. If treatment is started early in the development of the crisis, when ketonemic acidosis has been of short duration, the administration of insulin alone or with moderate amounts of salt solution may be sufficient to promote rapid recovery. Then the re-establishment of normal fluid and electrolyte equilibrium follows natural processes of realimentation. Fairly simple schemes of treatment³⁷ have led to good results even with severely comatose patients. Under critical conditions, however, the use of all available procedures for corrective therapy and of laboratory studies for their control should be carefully considered.

The following schedule for the treatment of coma is offered tentatively as a basis for further discussion of guiding principles and of current opinions that are held in different

centers regarding the use of the respective procedures.

i. Insulin may be administered in most cases in moderate doses (30 to 60 units per hour in adults, 10 to 20 units in small children) given in divided doses at short intervals, fifteen to sixty minutes, to assure a continuous supply and an overlapping of the effects of each dose. In unusual cases of insulin resistance larger doses will be required.

ii. Parenteral fluid therapy, comprising the administration of water, electrolytes, glucose, blood: (1) *physiologic salt* solutions given intravenously first (mixed with alkali as indicated), in amounts approximating 1 to 2 per cent of the body weight per hour during the first two or three hours, then more slowly; (2) *alkali*, as sodium bicarbonate or sodium lactate, given with the first intravenous fluids, as soon as the degree of acidosis is known, in amounts sufficient to bring the plasma pH to normal or to raise the plasma bicarbonate to around 13 m.Eq. per L., or 30 volumes per cent; (3) *glucose*, administered as 5 per cent solution in physiologic saline solution or in water, after the third to sixth hour of treatment, after the correction of acidosis with alkali and when the effectiveness of insulin is assured but without waiting for the blood sugar to fall to normal or hypoglycemic levels; (4) *potassium and phosphate salts*, administered cautiously intravenously or by mouth, after four to six hours, four doses of KCl, 1 Gm. each, hourly, anticipating hypopotassemia and cellular needs for replenishment in cases where severe depletion is suspected or known; (5) *whole blood or plasma transfusions*, indicated in cases with anemia, persistent circulatory collapse and shock, anuria.

iii. Vitamin preparations, especially of the B-complex, given in parenteral fluids and with oral realimentation.

iv. Chemotherapy, started promptly in the presence of infections.

v. Feeding by mouth should be started as early as possible, as soon as vomiting has ceased.

PROCEDURES

Insulin. There is unanimous agreement that insulin should be administered at once when the diagnosis of diabetic acidosis is made. But opinions differ widely on the dosage that should be employed during the first hours of treatment, as well as on the use of supportive treatment which may influence the effectiveness of insulin. Root and co-workers³⁸ recommend high initial doses of insulin, usually 100 units, with 300 or 500 units extra if the blood sugar is above 600 or 1000 mg. per 100 cc., to be followed by repeated doses at intervals depending on the results of clinical and laboratory tests. Among recommendations for the routine use of high doses perhaps the most extreme is that of Micks³⁹ who, claiming to follow Root's teaching, recommended an initial dose of 100 units for patients in pre-coma, 500 units for patients in true coma, followed by 100 units given (intravenously) every fifteen minutes until the appearance of clinical signs of improvement. Mick's scheme is like Root's in that the administration of insulin is accompanied only by intravenous perfusion of salt solution (4 to 6 L.) in the first few hours, with no glucose "until the blood sugar is low," and with no alkali used to correct the acidosis. This article elicited an editorial in the same journal⁴⁰ calling attention to the dangers from hypoglycemia likely to be incurred by such a procedure, also a note by Lawrence⁴¹ expressing objections and citing his own satisfactory experiences in treating patients "in severe pre-coma" with total dosage of 124 to 196 units in divided doses during sixteen to twenty-four hours.

Dangers of damage to the central nervous system by the effects of large doses of insulin must be borne in mind; although those who recommend large doses in the treatment of coma generally discount this possibility, trusting that the administration of glucose will arrest the progress of any deleterious reactions. Yannet^{42,43} found that large doses of insulin in cats led to demonstrable damage to the brain, with loss of potassium.

This effect was only partly attributable to hypoglycemia *per se* as larger doses produced more damage without notable differences in the degree or duration of hypoglycemia.

Overdosage with insulin may have other unfavorable effects not entirely disclosed by blood sugar levels. Somogyi⁴⁴ has pointed out that there are two phases in the action of insulin when given in a dosage sufficient to provoke hypoglycemia. In the first, excessive ketogenesis is arrested as liver glycogen increases and glycogenolysis is inhibited; in the second, with hypoglycemia, ketone formation increases as liver glycogen is again depleted by increased glycogenolysis. Thus during recovery from coma, after the elimination of ketosis there may be a "paradoxical" reappearance of ketonuria dependent upon the development of hypoglycemia. While such ketonuria is usually mild, secondary effects may be important. Mobilization of liver glycogen involves the liberation of potassium to plasma⁴⁵ which may add to the instability of potassium metabolism in this critical period of recovery.

Haste in the administration of very large doses of insulin merely to reduce the blood sugar quickly seems futile, considering the fact that varying degrees of hyperglycemia cannot be correlated with the severity of acidosis or the depth of narcosis in comatose patients. Maximum effectiveness of insulin in the reduction of ketosis may depend more upon supportive measures than upon the speed with which the blood sugar level is reduced.

Parenteral Fluids. Intravenous therapy is directed primarily to the correction of abnormalities in the extracellular fluids and to secure improvement in the circulating blood volume, secondarily to promote intracellular processes of recovery. There seems to be no valid reason for the use of the subcutaneous route for the administration of fluids except difficulty in venipuncture, and this difficulty should be rare. Fluid under the skin serves no useful purpose until it is absorbed into the circulation, and absorption is slowest in the patients with poorest circulation in whom the immediate

need for fluids to improve the blood volume is most urgent. In the regulation of dosage a working rule followed in our pediatric service is that the total volume of all fluids administered parenterally in the first eighteen to twenty-four hours of treatment may amount to between 10 and 15 per cent of the body weight, but with intravenous perfusion at the rate of 1 to 2 per cent of the body weight per hour during the first two or three hours. Intravenous perfusions should be discontinued promptly when the urine becomes ketone-free or nearly so and when fluids are taken well by mouth, trusting natural processes of realimentation to complete the restoration of metabolic equilibrium.

Salt Solutions. Practically all schemes for parenteral fluid therapy provide first for generous amounts of physiologic salt solution, usually 2 to 4 L. in adults, administered rapidly in the first few hours to cover primary extracellular needs for rehydration and continued at a slower rate in combination with glucose or with other salts.

Alkali. There are widely divergent differences of opinion on the advisability of administering sodium bicarbonate or sodium lactate for the correction of acidosis in the treatment of coma. Among those who object, some merely maintain that such therapy is unnecessary since the gradual elimination of ketosis by insulin leads to an increase of plasma bicarbonate without the addition of sodium. Others insist that it is potentially dangerous, citing cases in which the administration of alkali to raise the plasma bicarbonate from acidotic levels to normal was followed by states of severe alkalosis later in the recovery period; or, worse, cases in which severe alkalosis was induced when large doses of sodium bicarbonate were employed to "treat" acetoneuria under the mistaken idea that acetoneuria necessarily means acidosis. But, as many others have pointed out, the fact that overdosage of a drug can be harmful is not a contraindication to its more judicious use to secure a desired effect. Arguments favoring rapid correction of acidosis by the administration of alkali in one form or another may

be based on evidence, already discussed, that low plasma pH values are associated with increased tissue catabolism, breakdown of intracellular phosphorus compounds and losses of P and K in the urine. A recent report⁴⁶ of metabolic studies on diabetic subjects in severe acidosis and during recovery, treated with insulin, saline and glucose solutions, states that "*potassium continued to pour out of cells throughout these earlier hours of therapy.*" Losses of P and K in the urine that continue during the early hours of treatment may be ascribed to uncorrected acidosis. As early as 1922 Campbell⁴⁷ maintained that the administration of sodium bicarbonate in combination with the newly developed insulin therapy was desirable because it accelerated recovery from severe acidosis.

There is reason to believe that the action of insulin in the treatment of coma is inhibited by conditions of ketonemic acidosis and is favored by the administration of alkali. Kirk⁴⁸ described two cases of coma precipitated by infection and omission of insulin in which there was failure of response to initial doses of insulin. Admitted to the hospital in a pre-comatose state, drowsy but conscious, both patients rapidly became more comatose and more acidotic after the start of treatment with insulin and intravenous perfusion of salt solution. The administration of sodium bicarbonate solution was followed immediately by recovery of consciousness and by symptomatic improvement before more insulin was given. Both patients responded normally to subsequent moderate doses of insulin.

A report by Shephard⁴⁹ offers an interesting comparison with the one just cited. Shephard reported a case of severe coma, with treatment guided by Mick's recommendations,³⁹ in which 56,000 units of insulin were administered in twenty-six hours. A thirty-two year old man, previously taking 42 units of insulin a day, abruptly went into acidosis and coma when, with a cold, he did not eat and omitted his insulin. Deeply comatose when admitted to the hospital he failed to respond to 1,000 units

of insulin given in the first ten hours. Progressively larger doses were given, to a total of 56,080 units in twenty-six hours, after which time the blood sugar fell to 24 mg. per 100 cc. and he developed convulsions. Recovery followed the administration of glucose. The patient was discharged after a few days, again receiving only a moderate dosage of insulin for daily control. It seems likely (to this reviewer) that in this case the existing conditions of severe acidosis could account for the ineffectiveness of the insulin and that correction of the acidosis with alkali might have favored earlier effectiveness of the insulin.

Conditions of keto-acidosis may interfere with metabolic readjustments that are set in play by insulin apart from its blood-sugar-lowering effects. A report by Hedon⁵⁰ in 1927 describing dramatic effects of the administration of sodium bicarbonate to a diabetic dog in severe acidosis and coma is especially interesting in this connection. The dog had been maintained in good condition by injections of insulin for thirteen months after pancreatectomy. When insulin was withheld, the animal quickly developed intense glycosuria, polyuria, thirst, loss of weight, increasing ketosis and went into complete coma on the fifth day. Injections of insulin failed to revive the dog. After several hours acidosis was apparently increasing (blood CO₂ decreased to 11 volumes per cent) and the dog appeared moribund although the hyperglycemia was reduced and glycosuria ceased. Intravenous injections of sodium bicarbonate solution were followed within a short time by signs of revival. After four hours when the blood CO₂ had risen to 35 volumes per cent, the dog walked across the laboratory in search of food. With continuation of the usual injections of insulin complete recovery followed.

More compelling arguments for the use of alkali may be found in the report by Kety et al.¹² that in comatose patients lowered pH of the blood was closely correlated with depression of cerebral oxygen metabolism, which proved to be an im-

portant prognostic index of mortality. These investigators demonstrated that the arterial blood pH in comatose patients could be brought quickly to normal by intravenously injected doses of sodium bicarbonate just sufficient to raise the blood CO_2 content by only 10 or 15 volumes per cent. They point out that since large doses are not necessary to bring the pH to normal, much of the objection against the intravenous use of alkalis in the treatment of coma can be met.

If the factor of acidosis, lowered pH of the body fluids, is recognized as a critical one in tissue damage that increases with the duration of coma, its *early* correction appears to be one of the most important steps in rational therapy. But when correction of acidosis is practised, dosage should be carefully controlled. Continuous administration of alkalinizing solutions (e.g., mixtures of sodium chloride and sodium lactate) has not infrequently led to the development of alkalosis and edema during the recovery period. Formulas employed for the calculation of dosage of alkali⁵¹ are based principally on that of Van Slyke,⁵² assuming that administered sodium bicarbonate will be distributed in fluids constituting 0.7 L. for each Kg. of body weight. Although the use of this formula (essentially empiric in derivation) has been criticized on theoretic grounds,²⁹ it proves an extremely valuable aid for estimating amounts of alkali required to correct acidosis to within a range selected as desirable in a given case and to avoid overdosage. In our hospital we use the following formulas for estimating amounts of sodium bicarbonate (preferred) or sodium lactate required *to raise the plasma CO_2 content to between 10 and 15 m.Eq. per L., or to between 20 and 30 volumes per cent.*

1. To raise the plasma CO_2 content 1 m.Eq./L., give 0.058 Gm. of NaHCO_3 or 4.2 cc. of M/6 Na-lactate solution, per Kg. of body weight.
2. To raise the plasma CO_2 1 volume per cent, give 0.026 Gm. NaHCO_3 or 1.8 cc. of M/6 Na-lactate per Kg. of body weight.

Glucose. Current discussions on the use of glucose in the treatment of coma are mainly concerned with the time at which its intravenous administration should be started. All authorities agree that glucose should be administered after the first four to six hours when the blood sugar is falling to normal levels or below, although there is less agreement as to the amounts and manner of its administration after that time. Only a few pertinent points in the controversies that have been waged on this subject in the past need be recalled here.

Objections to the early administration of glucose have been based principally on claims that at hyperglycemic levels glucose is toxic, it injures islet cells of the pancreas, causes hepatic and renal damage, has been a precipitating cause of coma and neutralizes insulin action. Some of the arguments offered in favor of the early administration of glucose are: that prior to treatment of coma there is a considerable carbohydrate deficit which should be covered by energetic replacements; that carbohydrate starvation can aggravate the diabetic state; that with liver glycogen exhausted the total amount of available glucose in the body is not large despite hyperglycemia; that hypoglycemia should not be allowed to develop during insulin therapy because hypoglycemia accelerates glycogenolysis, again increasing ketogenesis; and that hyperglycemia favors hepatic glycogenesis and abolition of ketosis under certain conditions in diabetic subjects. The arguments and counterarguments on each of these points may be found in articles by Root,³⁸ Joslin et al.,²⁰ Peters,⁵³ Soskin,⁴ Mirsky,⁵⁴ Tolstoi,³⁷ Franks et al.⁵⁵ and Lee et al.⁵⁶

The physiologic evidence suggesting that early and generous administration of glucose in the treatment of coma would be beneficial appears to be sound. Nevertheless, a number of investigators have reported unfavorable results from this procedure in the treatment of severely comatose patients. Two widely separated groups of investigators⁵⁵⁻⁵⁶ compared the behavior of patients receiving perfusions of glucose solution during the

first four to six hours of treatment with that of patients receiving only saline solutions during the same period, carrying out essentially the same treatment in all of the patients after the initial period. Both groups report that the early administration of glucose solutions led to prolonged hyperglycemia, excessive diuresis, interfered with rapid rehydration and appeared to increase mortality significantly. In the interpretation of these reports it may be surmised that it was the diuretic effect of the glucose solutions that had unfavorable consequences, not any specific ill effect of the glucose itself within the body. Hypertonic solutions of glucose tend to aggravate diuresis more than isotonic solutions. In a series of cases of coma studied on the medical wards of the Cincinnati General Hospital the intravenous perfusion of 10 per cent glucose solution has been found to provoke severe diuresis, with urinary output sometimes nearly equal to the volume of fluids administered.⁵⁷

In the critical period just after the start of treatment, while acidosis persists and intracellular elements "continue to pour out of the cells"⁴⁶ into the plasma, any procedure leading to increased diuresis may be expected to increase the loss of electrolytes in the urine. The extra loss of electrolytes induced by increased diuresis, even for a short period, may indeed be just sufficient to influence mortality. Excessive diuresis at this time is likely to have more deleterious effects than later, after acidosis has been corrected and insulin promotes anabolic readjustments in the cells. If this speculation is valid, the reports that have been cited constitute an additional reason for the early administration of NaHCO_3 to correct acidosis quickly, as a step to precede the start of glucose therapy. Evidence of ill effects of the perfusion of glucose solutions during the first hours of treatment should not be allowed to detract from the validity of arguments favoring the generous administration of glucose later.

Multielectrolyte Therapy: Potassium, phosphates, etc. Numerous formulas have been devised for fluids that provide in different

ways for the correction of acidosis and for the supply of intracellular as well as the extracellular electrolytes.⁵⁸⁻⁶¹ A basic approach to this problem has been to employ mixtures of sodium chloride and sodium bicarbonate, or of sodium chloride and sodium lactate, to provide an excess of Na over Cl such as exists normally in extracellular fluids of the body, with other elements added according to different indications or opinions as to needs. Hartman employed a modified lactate-Ringer's solution to supply small amounts of K, Ca and Mg in addition to Na; in 1929 he added more potassium but this formula was temporarily abandoned "because sometimes the richer potassium solution seemed toxic."⁶¹ Interest in potassium therapy has, of course, been greatly stimulated by Darrow's studies on potassium metabolism in diarrheal disease of infants^{62, 63} and by many recent reports on the post-acidotic hypokalemia syndrome, which emphasize the significance of potassium deficits that had long been known to exist in diabetic acidosis.

With attention focused on phosphorus metabolism, Guest and Rapoport demonstrated that the administration of Na and K phosphates intravenously and by mouth hastened the restoration of normal concentrations of phosphoric esters in the blood cells of patients and experimental subjects during their recovery from ammonium chloride acidosis, from the acidosis of diarrheal disease in infants and from diabetic acidosis.^{27, 30, 31} We employed the Sørensen M/7.5 buffer solution, of pH 7.4, containing Na_2HPO_4 15.2 Gm. and KH_2PO_4 3.6 Gm. per L., with concentrations of Na and K, respectively, 214 and 26 m.Eq. per L. In the treatment of diabetic coma in adult patients this solution was perfused intravenously in amounts up to a liter, in combination with insulin, physiologic salt solution, sodium bicarbonate for partial correction of acidosis and glucose. Concentrations of organic acid-soluble P in the blood cells of these patients rose quickly to normal in less than twenty-four hours in contrast to the slow rise lasting four to seven days observed in other patients

similarly treated but without the phosphate solution. Concentrations of inorganic P and K in the plasma fell sharply in the early hours of treatment. The concentration of K in the cells rose closely in parallel with the increasing concentration of organic phosphates.

In 1948 Franks and co-workers described effects of the administration of a buffered solution of sodium phosphates in sixteen cases of severe diabetic acidosis, comparing the results with those observed in control subjects with fluid therapy limited to salt and glucose solutions.⁶⁴ They reported that "the administration of sodium phosphate was accompanied with a tendency toward improved utilization of carbohydrate, a rise in plasma chloride and in carbon-dioxide combining power, an apparent retention of fluid in the vascular system, a rapid clearing of the mental state and a statistically significant decrease in fatality rate." They concluded that the therapeutic regimen in diabetic coma should include parenteral administration of sodium phosphate four to eight hours after the first dose of insulin.

Butler and co-workers recently estimated the total electrolyte deficit of a volunteer subject going into severe acidosis following the withdrawal of insulin and during recovery.²⁹ On the basis of the metabolic balance data thus obtained they devised a formula for use in fluid and electrolyte replacement therapy that includes sodium lactate, potassium chloride, potassium phosphate and sodium chloride: 30 m.Eq. of Na, 20 m.Eq. of K, 22 m.Eq. of Cl, 5 m.Eq. of phosphate and 20 m.Eq. of lactate per L. in a solution of 5 per cent glucose. This approach seems logical but, as these investigators themselves state, before such therapy can be applied quantitatively more information is needed.

In addition to metabolic data on total losses of electrolytes in acidosis and on the eventual uptake of electrolytes by the body during recovery, there is need for more knowledge of the conditions that determine the changing ability of the tissue cells to assimilate various materials that are offered.

The transfer of potassium and phosphate ions to cells is not so much dependent on their concentration in the plasma as upon enzymatic processes, which in turn are subject to the influence of changing conditions in the body fluids.

There is abundant evidence that the depleted body recovering from diabetic acidosis, given the right conditions, is capable of taking up large quantities of intravenously injected potassium salts without an abnormal rise in concentration of potassium in the plasma. Howard and Carcy⁶⁵ mention an instance in which 35 Gm. of KCl (467 m.Eq. of K) were injected into a patient in eighteen hours and less than 100 m.Eq. appeared in the urine. On the other hand, deaths have occurred from the incautious administration of much smaller amounts. All investigators studying this problem caution against the dangers of hyperpotassemia arising if solutions of potassium salts are administered too rapidly or too early in the treatment of coma, when the plasma potassium level is elevated, especially in the presence of renal impairment.

In the treatment of severely comatose patients when even without complete chemical studies the need for potassium is reasonably certain, it seems desirable and safe to administer 1 Gm. of KCl each hour for four doses, as now practiced in a number of centers. The first dose may be started at around the fourth hour of treatment, after acidosis has been partially corrected by the administration of sodium bicarbonate and when insulin is becoming increasingly effective. Since relatively small amounts of KCl have afforded prompt relief of severe symptoms of respiratory paralysis, as in Holler's original case, conservative dosage of this sort should suffice in most cases to prevent any acute manifestation of potassium deficiency. The time at which minimal corrective therapy is offered, if properly directed to negotiate each critical phase in coma and recovery, may be more important than speed in the replenishment of total deficits. After a patient has successfully passed through the critical early period of

recovery further restoration of the body stores and a more normal nutritional state can be accomplished efficiently by oral feeding.

Whole Blood and/or Plasma. The problems of the restoration of circulating blood volume in the treatment of severe coma with circulatory collapse are similar to those encountered in the treatment of surgical shock. When acidosis has been of short duration and dehydration abrupt, in patients whose previous nutritional state was good, hematocrit values and concentrations of plasma protein are apt to be high, indicating hemoconcentration. In such cases the administration of salt solution serves adequately to restore the circulating plasma volume. But if the concentration of plasma protein is normal or low at the start of treatment, it may fall sharply with dilution and the perfused salt solution may tend to leave the circulation. In such circumstances, and in any case if the blood pressure does not respond to the administration of saline fluids, whole blood or plasma transfusions should be administered promptly. This need is encountered more frequently in older patients than in young adults, rarely in children, in our experience.

Vitamins. Several factors of the vitamin B-complex (thiamine, riboflavin, niacin) are essential to the enzyme systems involved in carbohydrate metabolism. Although there is no reason to believe that vitamin deficiencies are concerned in the etiology of diabetes, mutually aggravating factors can be defined in the metabolic disturbances of co-existent diabetes and avitaminosis.⁶⁶ Vitamin deficiencies in diabetic subjects lead to increased needs for insulin; on the other hand, the stimulation of carbohydrate metabolism by the administration of insulin and glucose in the treatment of coma abruptly increases the body's needs for the vitamins. A diabetic crisis, coma and recovery may precipitate frank manifestations of avitaminosis in subjects with previously unrecognized deficiency states, with symptoms usually blossoming during periods of increased food intake and rapid gain of

weight. Hence, it is a well justified common practice in many clinics to administer multi-vitamin B preparations with intravenous fluids during the treatment of coma and to continue generous amounts by mouth, supplementing realimentation in the recovery period. Inasmuch as phosphorylation of the vitamins into active forms in the body may be slow in diabetic acidosis,⁶⁷ it has been suggested that the use of phosphorylated preparations (when available) might be more quickly effective. Boulin, Uhry and co-workers^{24a} and Markus and Meyer^{24b} have reported the use of a crystalline preparation of thiamine-pyrophosphate (cocarboxylase) in the treatment of coma. These authors offer the thesis that an important disturbance of carbohydrate metabolism in diabetic coma is involved at a stage in the Krebs tricarboxylic acid cycle in which insulin is not involved but cocarboxylase is essential for the conversion of pyruvate; that the difficulty at this stage accounts for the finding of high blood-pyruvate levels in diabetic coma and that slowing of the disposal of pyruvate interferes with other phases of carbohydrate metabolism in which insulin is involved. They claim for the scheme of treatment in which cocarboxylase was employed (100 mg. cocarboxylase plus 10 mg. riboflavin) some reduction in the duration of coma and a considerable reduction in total requirements for insulin (in a small series of ten patients) compared with results previously obtained in the same clinic.

The Prevention of Diabetic Acidosis and Coma. Under any system of diabetic control, whether with rigid regimentation of a "prescribed-diet-aglycosuric regimen," or with liberal rules of the so-called "free-diet-glycosuric regimen," instructions for home management should emphasize unceasingly the signs of impending trouble to which the patients (or parents of young diabetics) should be alert: excessive diuresis, loss of weight and acetoneuria. Rapidly increasing ketonuria is the most dependable sign heralding the incipient development of a diabetic crisis, more dependable than glycosuria as an index of the physiologic state of

the liver with regard to its glycogen store and cellular metabolism. Frequent testing of the urine for acetone should be an essential part of any scheme for self-management. Use of the convenient acetone-test powders⁶⁸ that are now commercially available makes this test easy, the least onerous task of the patient's daily routine at home or elsewhere.

It is especially urgent that tests of the urine for acetone be done during any illness, whether mild or severe, with respiratory and gastrointestinal infections, diarrhea, vomiting, fever, the contagious diseases of childhood, etc.; also, at times of physical injuries, unusual excitement, emotional stress. When acetonuria is discovered under any of these circumstances, extra insulin should be taken promptly. The development of a crisis can be more easily arrested by extra doses of insulin when acetonuria first appears than later when the progressive development of acidosis involves factors that diminish the effectiveness of insulin.

REFERENCES

1. WHITE, P. and WASKOW, E. Arteriosclerosis in childhood diabetes. *Proc. Am. Diabetes A.*, 8: 139, 1948.
2. AXELROD, A. R., LOBE, S., ORTEN, J. M. and MYERS, G. B. Insulin resistance. *Ann. Int. Med.*, 27: 555, 1947.
3. SMOLO, L. S. Insulin resistance. *Proc. Am. Diabetes A.*, 8: 75, 1948.
4. SOSKIN, S. and LEVINE, R. Carbohydrate Metabolism. Chap. 21, p. 247. Chicago, 1946. University of Chicago Press.
5. ZILVERSMIT, D. B., CHAIKOFF, I. L., FELLER, D. D. and MASORO, E. J. Oxidation of glucose labelled with radioactive carbon by normal and alloxan-diabetic rats. *J. Biol. Chem.*, 176: 389, 1948.
6. MIRSKY, I. A., FRANZBLAU, A. N., NELSON, N. and NELSON, W. E. Diabetes mellitus. The role of excessive carbohydrate intake in the etiology of diabetic coma. *J. Clin. Endocrinol.*, 1: 307, 1941.
7. RAPOPORT, S., WEST, C. D. and BRODSKY, W. A. Excretion of solutes and osmotic work during osmotic diuresis of hydropenic man. The ideal and the proximal and distal tubular work; the biological maximum of work. *Am. J. Physiol.*, 157: 363, 1949.
8. STADIE, W. C., ZAPP, J. A., JR. and LUKENS, F. D. W. Effect of insulin upon ketone metabolism of normal and diabetic cats. *J. Biol. Chem.*, 132: 423, 1940.
9. STADIE, W. C. Fat metabolism in diabetes mellitus. *J. Clin. Investigation*, 19: 843, 1940.
10. CHAIKOFF, I. L. and SOSKIN, S. The utilization of acetoacetic acid by normal and diabetic dogs before and after evisceration. *Am. J. Physiol.*, 87: 58, 1928.
11. NELSON, N., GRAYMAN, I. and MIRSKY, I. A. The utilization of acetone bodies. iv. The relation between concentration and the rate of β -hydroxybutyric acid utilization by the rat. *J. Biol. Chem.*, 140: 361, 1941.
12. KETY, S. S., POLIS, B. D., NADLER, C. S. and SCHMIDT, C. F. The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. *J. Clin. Investigation*, 27: 500, 1948.
13. ATCHLEY, D. W., LOEB, R. F., RICHARDS, D. W., JR., BENEDICT, E. M. and DRISCOLL, M. E. On diabetic acidosis: a detailed study of electrolyte balances following withdrawal and reestablishment of insulin therapy. *J. Clin. Investigation*, 12: 297, 1933.
14. PITTS, R. F. and ALEXANDER, R. S. The renal reabsorptive mechanism for inorganic phosphate in normal and acidotic dogs. *Am. J. Physiol.*, 142: 648, 1944.
15. RAPOPORT, S. Hyperosmolarity and hyper electrolytemia in pathologic conditions of childhood. *Am. J. Dis. Child.*, 74: 682, 1947.
16. BAKER, T. W. A clinical survey of one hundred and eight consecutive cases of diabetic coma. *Arch. Int. Med.*, 58: 373, 1936.
17. OWENS, L. B. and ROCKWERN, S. Prognosis in diabetic coma: basic importance of mental state. *Am. J. M. Sc.*, 198: 252, 1939.
18. DILLON, E. S. and DYER, W. W. Factors influencing the prognosis in diabetic coma. *Ann. Int. Med.*, 11: 602, 1937.
19. JOSLIN, E. P., ROOT, H. F., WHITE, P. and MARBLE, A. Diabetic coma. *J. A. M. A.*, 119: 1160, 1942.
20. JOSLIN, E. P., ROOT, H. F., WHITE, P., MARBLE, A. and BAILEY, C. C. The Treatment of Diabetes Mellitus. Philadelphia, 1946. Lea and Febiger.
21. NADLER, C. S., BELLET, S. and LANNING, M. Influence of the serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. *Am. J. Med.*, 5: 838, 1948.
22. GORANSON, E. S. Reduced synthesis of phosphocreatinine in tissue homogenates from alloxan diabetic rats. *Federation Proc., Am. Physiol. Soc.*, 8: 58, 1949.
- 23a. BOUCKAERT, J. P. and DE DUVE, C. The action of insulin. *Physiol. Rev.*, 27: 39, 1947.
- 23b. LUNDGAARD, E. Muscle and insulin metabolism. Proceedings, 2nd International Congress of Therapeutics, Brussels, Belgium, June 10-11, 1949. (Unpublished.)
- 24a. BOULIN, R., UHRY, P., MEYER, F. W. and BONFILS, S. Essai de traitement du coma diabétique en fonction des données biochimiques du métabolisme des glucides. *Presse méd.*, 57: 689, 1949.
- 24b. MARKUS, S. and MEYER, F. W. Die Therapie des Coma diabeticum mit Cocarboxylase. *Schweiz. med. Wchnschr.*, 1949 (in press).
25. GUEST, G. M. and RAPOPORT, S. Organic acid-soluble phosphorus compounds of the blood. *Physiol. Rev.*, 21: 410, 1941.
26. GUEST, G. M. and RAPOPORT, S. Role of diphosphoglycerate and other organic acid-soluble phosphorus compounds of the red blood cells in the electrolyte equilibrium of the blood. American

- Association for the Advancement of Science, Symposium, Blood, Heart and Circulation. No. 13, pp. 55-60. New York, 1940. Science Press.
27. GUEST, G. M. and RAPOPORT, S. Role of acid-soluble phosphorus compounds in red blood cells in experimental rickets, renal insufficiency, pyloric obstruction, gastroenteritis, ammonium chloride acidosis and diabetic acidosis. *Am. J. Dis. Child.*, 58: 1072, 1939.
 28. RAPOPORT, S. and GUEST, G. M. The decomposition of diphosphoglycerate in acidified blood: its relationship to reactions of the glycolytic cycle. *J. Biol. Chem.*, 129: 781, 1939.
 29. BUTLER, A. M., TALBOT, N. B., BURNETT, C. H., STANBURY, J. B. and MACLACHLAN, E. A. Metabolic studies in diabetic coma. *Tr. A. Am. Physicians*, 60: 102, 1947.
 30. GUEST, G. M. Organic phosphates of the blood and mineral metabolism in diabetic acidosis. *Am. J. Dis. Child.*, 64: 401, 1942.
 31. GUEST, G. M. and RAPOPORT, S. Electrolytes of blood plasma and cells in diabetic acidosis and during recovery. *Proc. Am. Diabetes A.*, 7: 97, 1947.
 32. HOLLER, J. W. Potassium deficiency occurring during the treatment of diabetic acidosis. *J. A. M. A.*, 131: 1186, 1946.
 33. NADLER, C. S., BELLET, S., DILLON, E. S. and LANNING, M. Studies on the serum potassium in diabetic acidosis. *Proc. Am. Diabetes A.* (In press.)
 34. FRENKEL, M., GROEN, J. and WILLEBRANDS, A. F. Low potassium level during recovery from diabetic coma. *Arch. Int. Med.*, 80: 728, 1947.
 35. MARTIN, H. E. and WERTMAN, M. Serum potassium, magnesium and calcium levels in diabetic acidosis. *J. Clin. Investigation*, 26: 217, 1947.
 36. RAPOPORT, S., DODD, K., CLARK, M. and SYLLM, I. Post-acidotic state of infantile diarrhea: symptoms and chemical data. *Am. J. Dis. Child.*, 73: 391, 1947.
 37. ALMY, T. P., SWIFT, K. and TOLSTOI, E. Treatment of diabetic acidosis and diabetic coma. *J. A. M. A.*, 129: 863, 1945.
 38. ROOT, H. F. The use of insulin and the abuse of glucose in the treatment of diabetic coma. *J. A. M. A.*, 127: 557, 1945.
 39. MICKS, R. H. Diabetic coma. *Brit. M. J.*, 2: 200, 1948.
 40. Editorial. Modern views on diabetes. *Brit. M. J.*, 2: 209, 1948.
 41. LAWRENCE, R. D. and OAKLEY, W. Diabetic coma. *Brit. M. J.*, 2: 310, 1948.
 42. YANNET, H. Effect of prolonged insulin hypoglycemia on distribution of water and electrolytes in brain and in muscle. *Arch. Neurol. & Psychiat.*, 42: 237, 1939.
 43. YANNET, H. Experimental study of pathogenesis of cerebral changes following prolonged insulin hypoglycemia. *Arch. Neurol. & Psychiat.*, 42: 395, 1939.
 44. SOMOGYI, M. Effects of insulin upon the production of ketone bodies. *J. Biol. Chem.*, 141: 219, 1941.
 45. FENN, W. O. The role of potassium in physiological processes. *Physiol. Rev.*, 20: 377, 1940.
 46. GREENMAN, L., MATEER, F. M., GOW, R. C., PETERS, J. H. and DANOWSKI, T. S. Some observations on the development of hypokalemia during therapy of diabetic acidosis in juvenile and young diabetic subjects. *J. Clin. Investigation*, 28: 409, 1949.
 47. CAMPBELL, W. R. Ketosis, acidosis and coma treated by insulin. *J. Metab. Research*, 2: 605, 1922.
 48. KIRK, E. Isotonic sodium bicarbonate solution in diabetic coma. *Lancet*, 1: 505, 1939.
 49. SHEPPARD, J. G. H. A case of diabetic coma treated with 56,000 units of insulin. *Brit. M. J.*, 1: 576, 1949.
 50. HEDON, M. E. La survie du chien totalement dépancréaté traité par l'insuline et les effets de l'interruption du traitement. *J. de physiol. et de path. gén.*, 25: 1, 1927.
 51. HARTMAN, A. F. and ERGANIAN, J. Treatment of diabetic acidosis. *J. Pediat.*, 31: 274, 1947.
 52. VAN SLYKE, D. D. Acidosis and alkalosis. *Bull. New York Acad. Med.*, 10: 103, 1934.
 53. PETERS, J. P. Starvation diabetes, the reason for the use of glucose in the treatment of diabetic acidosis. *Yale J. Biol. & Med.*, 17: 705, 1945.
 54. MIRSKY, I. A. The etiology of diabetic acidosis. *Proc. Am. Diabetes A.*, 1: 51, 1941.
 55. FRANKS, M., BERRIS, R. F., KAPLAN, N. O. and MYERS, G. B. Metabolic studies in diabetic acidosis. I. The effect of the early administration of dextrose. *Arch. Int. Med.*, 80: 739, 1947.
 56. LEE, J., NAIDOO, D. and TORRENS, J. A. Diabetic coma: treatment with and without the early administration of glucose. *Brit. M. J.*, 1: 565, 1949.
 57. KNOWLES, H. Personal communication.
 58. BURNETT, C. H. and BURROWS, B. A. Repair solutions in the treatment of metabolic acidosis and alkalosis. *M. Clin. North America*, 32: 1293, 1948.
 59. SPRAGUE, R. G. Diabetic acidosis and coma. *M. Clin. North America*, 31: 445, 1947.
 60. BUTLER, A. M. and TALBOT, N. B. Parenteral fluid therapy. *New England J. Med.*, 231: 585-590, 621-628, 1944.
 61. DARROW, D. C. The pharmacopeia and the physician: treatment of dehydration, acidosis and alkalosis. *J. A. M. A.*, 114: 655, 1940.
 62. DARROW, D. C. The retention of electrolyte during recovery from severe dehydration due to diarrhea. *J. Pediat.*, 28: 515, 1946.
 63. GOVAN, C. D. and DARROW, D. C. The use of potassium chloride in the treatment of the dehydration of diarrhea in infants. *J. Pediat.*, 28: 541, 1946.
 64. FRANKS, M., BERRIS, R. F., KAPLAN, N. O. and MYERS, G. B. Metabolic studies in diabetic acidosis. II. The effect of the administration of sodium phosphate. *Arch. Int. Med.*, 81: 42, 1948.
 65. HOWARD, J. E. and CAREY, R. A. The use of potassium in therapy. *J. Clin. Endocrinol.*, 9: 691, 1949.
 66. GUEST, G. M. Nutrition in diabetes mellitus. *Nutrition Rev.*, 4: 321, 1946.
 67. VILTER, R. W., VILTER, S. P. and SPIES, T. D. Determination of the cohydrogenases I and II (cozymase) in the blood of diabetics in severe acidosis. *Am. J. M. Sc.*, 197: 322, 1939.
 68. DUMM, R. M. and SHIPLEY, R. A. The simple estimation of blood ketones in diabetic acidosis. *J. Lab. & Clin. Med.*, 31: 1162, 1946.

Changes in the Volume of the Plasma, Interstitial and Intracellular Fluid Spaces During Hydration and Dehydration in Normal and Edematous Subjects*

SAMUEL E. LEARD, M.D. and EDWARD D. FREIS, M.D.

Boston, Massachusetts

RECENT investigations indicate that both the plasma volume¹⁻⁵ and the intracellular fluid space^{6,7} are responsive to changes in hydration. These observations are in opposition to the concept that the "losses of extracellular fluid from the vascular compartment caused by abnormal circumstances are observed to be immediately replaced at the expense of interstitial fluid."⁸

The present investigation was undertaken to determine the extent of the contribution of each fluid compartment to the gain or loss of total body water during states of excessive hydration or dehydration in normal subjects and after diuresis in edematous patients. In addition changes in the hematocrit and plasma protein concentration were assessed as to their reliability in predicting changes in plasma volume during fluctuations in hydration.

MATERIAL AND METHODS

The normal subjects were young adult males admitted to the wards of the Evans Memorial Hospital for treatment of uncomplicated latent or primary syphilis. All subjects were afebrile and exhibited no cardiovascular or renal abnormalities. The edematous patients comprised a heterogeneous group with various diagnoses. (Table I.)

Immediately following control determinations

in both normal and edematous subjects, dehydration was carried out by instituting a regimen of fluid restriction to 1,000 cc. daily, a diet containing a total of 0.8 Gm. of sodium per day and administration of 6 Gm. of ammonium chloride daily. On the evening of the fourth day 2 cc. of mercurhydrin were injected intravenously and the experimental observations were repeated on the morning of the fifth day.

Excessive hydration was produced in normal subjects by administering daily doses of 25 Gm. of sodium chloride orally and 10 mg. of desoxycorticosterone acetate intramuscularly for a period of five days with fluids and diet *ad libitum*. Control determinations were accomplished immediately prior to the institution of this regimen, and experimental observations were carried out on the morning of the fifth day. In three of these subjects 2 cc. of mercurpurin were injected intravenously on the evening of the fifth day followed by a further series of experimental observations on the morning of the sixth day.

The methods used for determining plasma volume, plasma protein, hematocrit value and "thiocyanate space" have been previously reported⁹ except that in the edematous patients a period of six rather than two hours was allowed for equilibration of thiocyanate. The thiocyanate space represents the total volume in which thiocyanate is distributed, including the plasma, red cells and interstitial fluid. Although thiocyanate measures a larger space than that actually occupied by the extracellular

* From the Evans Memorial, Massachusetts Memorial Hospitals and the Department of Medicine, Boston University Medical School, Boston, Mass. This investigation was supported in part by the Squibb Institute for Medical Research, New Brunswick, N. J.

fluid volume, other methods available to clinical medicine, such as the chloride and sodium spaces, suffer from similar disad-

stances during acute experiments probably represent gains or losses of extracellular fluid. Because of the simplicity of the thiocyanate

TABLE 1

THE CHANGES IN PLASMA VOLUME AND TOTAL EXTRACELLULAR (AVAILABLE) FLUID FOLLOWING HYDRATING AND DEHYDRATING PROCEDURES IN NORMAL INDIVIDUALS AND IN PATIENTS WITH DISTURBED WATER BALANCE

Subject	Age	Diagnosis	Procedure	Plasma Volume (cc.)			Available Fluid (cc.)			Plasma Volume Change
				Before	After	Gain or Loss	Before	After	Gain or Loss	Available Fluid Change
J. D.	20	Primary syphilis	Dehydration*	2970	2760	-210	20,250	19,250	-1000	.21
E. L.	28	Primary syphilis	Dehydration*	3590	2490	-1100	20,200	17,800	-2400	.46
J. G.	23	Latent syphilis	Dehydration*	2820	2240	-580	19,800	19,200	-600	.97
V. B.	23	Primary syphilis	Dehydration*	3300	2960	-335	17,250	15,900	-1350	.25
						-555			-1340	.47
D. J.	72	Hypertension, cardiac failure	Dehydration†	3450	2775	-675	34,600	16,650	-17,950	.04
D. E.	40	Cirrhosis, ascites	Dehydration†	4940	4700	-240	34,200	28,500	-5700	.04
B. G.	58	Hypertension, Paget's disease, cardiac failure	Dehydration†	3090	2695	-315	33,400	14,700	-18,700	.01
C. F.	74	Chronic nephritis, cardiac failure	Dehydration†	4270	3580	-690	29,400	22,900	-6500	.11
						-480			-12,210	.05
W. S.	24	Primary syphilis	Hydration‡	2820	3420	+600	21,500	24,800	+3300	.18
R. L.	37	Latent syphilis	Hydration‡	3010	3600	+590	21,650	28,100	+6450	.09
E. N.	31	Primary syphilis	Hydration‡	3330	3690	+360	17,400	20,800	+3400	.11
A. L.	30	Primary syphilis	Hydration‡	3120	3690	+570	19,400	24,800	+5400	.11
						+525			+4640	.72
R. L.	37	Latent syphilis	Dehydration§	3600	3000	-600	28,100	22,500	-5600	.11
E. N.	31	Primary syphilis	Dehydration§	3690	3260	-430	20,800	16,450	-4400	.10
A. L.	30	Primary syphilis	Dehydration§	3690	2945	-745	24,800	17,250	-7550	.10
						-410			-5850	.70

* Normal subjects dehydrated with low sodium diet, NH_4Cl and mercurhydrin.

† Edematous patients dehydrated with low sodium diet, NH_4Cl and mercurhydrin

‡ Normal subjects hydrated with excess sodium chloride and desoxycorticosterone acetate.

§ Normal subjects previously hydrated as in ‡ acutely dehydrated with single dose of mercurhydrin.

|| This value expresses the per cent gain or loss of total extracellular (available) fluid contributed to by the change in the plasma volume.

(Mean values in italics.)

vantages.¹⁰ Furthermore, since the cellular elements which all of these electrolytes enter change in volume very slowly, the changes observed in the volume distribution of such

method, it has greater advantage in clinical studies than other methods. Until such time as practical and accurate measurements of extracellular fluid volume are devised, the methods

used in this study must suffice with the realization that they are at best crude indicators of quantitative changes.

The difference between the changes in the thiocyanate space and the plasma volume after hydration or dehydration represented the changes in the interstitial fluid space. Because of the absence of methods of determining the intracellular fluid space directly in man, the difference between the change in body weight in Kg. and the thiocyanate space in L. was used to calculate the change in intracellular fluid volume. It was assumed that since these patients were not acutely ill their food intake and tissue breakdown were relatively constant during the experiment and therefore the changes in weight represented almost entirely changes in total body water. Further, the experimental periods were never greater than five days. Again, the changes observed in intracellular fluid space should be considered as representing approximate rather than precise numerical values.

All determinations were carried out in the morning with the patient in the postabsorptive state, resting supine in a warm room for at least one-half hour prior to drawing the first blood samples; venipunctures were accomplished with minimal stasis. After these determinations were completed the arterial pressure was recorded with an arm cuff and the subjects were weighed on a beam balance accurate to ± 2 Gm.

RESULTS

Relative Changes in Plasma Volume and Interstitial Fluid Space. When four normal subjects were dehydrated by the method just described, the mean decrease in plasma volume was 555 cc. (range 210 to 1,100 cc.) while the mean reduction in total extracellular (thiocyanate) space was 1,340 cc. (range 600 to 2,400 cc.). Thus the plasma volume contributed an average of 47 per cent of the decrease in total extracellular fluid (range 21 to 97 per cent).

In the four edematous patients subjected to the same regimen of dehydration the plasma volume contributed only 4 to 11 per cent (mean 5 per cent) of the decrease in the thiocyanate space. The absolute decrease of 240 to 690 cc. (mean 480 cc.) in plasma volume was approximately the same as in

the normal subjects but the reduction in the thiocyanate space was almost ten times as great (Table I) ranging from 5,700 to 18,700 cc. with a mean of 12,210 cc.

When four normal subjects were overly hydrated with an excess of salt and desoxycorticosterone acetate, the thiocyanate space increased by 3,300 to 6,450 cc. (mean 4,640 cc.). Again the mean increase in plasma volume of 527 cc. (range 360 to 600 cc.) gained during excessive hydration was quite similar in amount to the mean decrease in plasma volume during dehydration. However, due to the apparently marked gain in interstitial fluid the increase in plasma volume made up only 9 to 19 per cent (mean 12 per cent) of the change in the total extracellular (thiocyanate) space.

When three normal subjects thus excessively hydrated were subjected to a sudden diuresis by an intravenous administration of mercupurin, the plasma volume and thiocyanate space decreased in almost exact proportion as they had increased. As a result the plasma volume contributed 10 to 11 per cent of the decrease in the "total extracellular space," in contrast to the much greater percentage contribution made by the plasma volume when normally hydrated individuals were dehydrated. (Table I.)

Relative Changes in Total Extracellular and Intracellular Fluid Spaces. The four normal subjects who were dehydrated by the regimen just described lost 0.6 to 2.4 L. of fluid (mean 1.3 L.), from the total extracellular (thiocyanate) space. (Table II.) During this period the loss of body weight ranged from 2.1 to 2.9 Kg. with a mean of 2.6 Kg. Since 1 L. of fluid weighs 1 Kg., the difference between the amount of weight loss in Kg. and the total extracellular fluid loss in L. was taken to represent approximately the change in intracellular fluid space. Calculated thus the intracellular fluid space decreased by 0.5 to 2.2 L. (mean 1.2 L.). The proportion of total body water loss contributed by the total extracellular fluids varied from 22 to 83 per cent (mean 52 per cent), the remainder

presumably being made up from the intracellular fluid space.

In edematous patients similar dehydrating procedures produced far greater drains in extracellular fluid. The thiocyanate space decreased by 5.7 to 18.7 L. (mean 12.2 L.)

the body weight decreased by the lesser amount of 14.9 Kg. In the remaining patients the intracellular losses of 2.0 to 4.75 L. were slightly greater than the decreases in the non-edematous normal individuals. However, due to the greater changes in

TABLE II
CHANGES IN TOTAL EXTRACELLULAR (AVAILABLE) FLUID AND BODY WEIGHT FOLLOWING HYDRATING AND DEHYDRATING PROCEDURES IN NORMAL INDIVIDUALS AND IN PATIENTS WITH DISTURBED WATER BALANCE

Subject	Body Weight (Kg.)			Available Fluid Gain or Loss Liters	Calculated Intracellular Fluid Gain or Loss (L.)	Available Fluid Change¶ Body Weight Change
	Before	After	Gain or Loss			
J. D.*	72.7	70.2	-2.5	-1.0	-1.5	0.40
E. L.*	65.7	62.8	-2.9	-2.4	-0.5	0.83
J. G.*	74.4	71.6	-2.8	-0.6	-2.2	0.22
V. B.*	62.5	60.4	-2.1	-1.35	-0.75	0.64
Mean			-2.6	-1.3	-1.3	0.52
D. J.†	63.2	40.5	-22.7	-17.95	-4.75	0.79
D. E.†	84.6	76.9	-7.7	-5.7	-2.0	0.74
B. G.†	51.4	36.5	-14.9	-18.7	+3.8	1.26
C. O.†	75.2	66.1	-9.1	-6.5	-2.6	0.72
Mean			-13.6	-12.2	-1.4	0.88
W. S.‡	72.4	75.5	+3.1	+3.3	-0.2	1.06
R. L.‡	80.2	84.0	+3.8	+6.45	-2.65	1.70
E. N.‡	61.2	63.9	+2.7	+3.4	-0.7	1.26
A. L.‡	72.6	75.8	+3.2	+5.4	-2.2	1.68
Mean			+3.2	+4.6	-1.9	1.67
R. L.§	84.0	79.2	-4.8	-5.6	+0.8	1.17
E. N.§	63.9	60.6	-3.3	-4.4	+1.1	1.33
A. L.§	75.8	72.1	-3.7	-7.55	+3.85	2.04
Mean			-3.9	-5.85	+1.9	1.13

*, †, ‡, §, same notations as in Table I.

|| Values derived from Table I.

¶ Expresses the per cent of weight gain or loss contributed by the change in total extracellular (available) fluid.

while body weight decreased by 7.7 to 22.7 Kg. (mean 13.6 Kg.). The total extracellular (thiocyanate) space contributed 72 to 126 per cent (mean 88 per cent) of the change in total body water. (Table II.) In patient B. G., Table II, almost 4 L. of fluid appeared to move into cells since the thiocyanate space decreased 18.7 L. while

the thiocyanate space in the edematous patients, the proportionate loss of intracellular fluid averaged only 22 per cent of the total body water as contrasted to 48 per cent in the normal subjects.

The excessive hydration produced in normal subjects by administration of salt and desoxycorticosterone acetate appeared

to result in a movement of fluid out of the intracellular into the extracellular space. Thus, whereas the mean increase in the thiocyanate space was 4.6 L. (range 3.3 to 5.45 L.) the mean increase in body weight was only 3.2 Kg. (range 2.7 to 3.8 Kg.). The apparent decrease in intracellular fluid, therefore, averaged 1.9 L. with a range of 0.2 to 2.65 L.

However, when mercurhydrin was administered intravenously to these overly hydrated subjects, the fluid shifts were such as to restore within twelve hours the approximate pretreatment control conditions. In the three subjects studied the mean decrease in thiocyanate space was 5.85 L. (range 4.4 to 7.55 L.) and body weight was 3.9 Kg. (range 3.3 to 4.8 Kg.), an apparent mean gain in intracellular fluid volume of 1.9 L. (range 0.8 to 3.85 L.). Thus mercurpurin appeared to be a specific antagonist of the salt and desoxycorticosterone acetate effect.

Relation of Changes in Hematocrit Value and Plasma Protein Concentration to Changes in Plasma Volume. To calculate the change in plasma volume from the hematocrit values the following formula was used:

$$\Delta PV = \frac{H_1 - H_2}{H_2(1 - H_1)}$$

ΔPV represents the change in plasma volume, H_1 the original hematocrit and H_2 the hematocrit value following dehydration or hydration. The ratio of the per cent change in plasma volume as determined by the dye method to the per cent change as calculated from the hematocrit values varied from unity by 0.4 to 2.12 (mean 0.93, S.D. 0.24). The correlation coefficient calculated from the equation

$$r = \frac{\Sigma x_1 x_2}{\sqrt{(\Sigma x_1^2)(\Sigma x_2^2)}}$$

was 0.49. Thus, although the change in hematocrit value indicated the directional change in plasma volume in every instance, it failed to determine quantitative change accurately.

The ratio of the per cent change in plasma volume to the per cent change in plasma protein varied from unity by 0.5 to 1.6 (mean 1.3, S.D. 0.18). The correlation coefficient was 0.68. The change in plasma protein concentration, therefore, seemed to indicate the degree of plasma volume change more accurately than the hematocrit. However, the agreement was not sufficiently close to warrant quantitative estimation.

Changes in Arterial Pressure. In the dehydrated subjects no significant changes in arterial pressure were noted in the supine position although one patient complained of faintness in the erect position following diuresis.¹¹ In all of the normal subjects who were given salt and DCA in excess, the supine mean arterial (one-half the sum of the systolic and diastolic) pressure rose slightly, the mean rise being 10.6 per cent (range 6.7 to 15.2 per cent).

COMMENTS

The results of this investigation suggest that neither the plasma volume nor the intracellular fluid volume are static under conditions of changing hydration. During dehydration in normal subjects approximately 25 per cent of the loss of total body water was contributed by the plasma volume, 25 per cent by the interstitial fluid and 50 per cent by the intracellular fluid. Mellers, Muntwyler, Meutz and Abbot² also observed a marked reduction of plasma volume in dogs who were dehydrated by various procedures including the intraperitoneal injection of 5 per cent glucose, starvation and the production of pancreatic fistulas.

In contrast, similar dehydrating procedures in patients with gross edema produced a loss of total body water of which approximately 5 per cent was supplied by the plasma volume, 85 per cent by the interstitial fluid and 10 per cent by the intracellular fluid. However, despite the smaller percentage changes of plasma and intracellular fluid volumes the absolute amount of fluid loss from these compart-

ments usually was approximately the same in both the normal and the edematous subjects, the difference in proportion being due to the far greater absolute losses of interstitial fluid in the edematous patients. It is evident that with the greater diuresis in edematous as contrasted to normal individuals the plasma volume must contribute a smaller percentile loss to the fluid depletion of edematous subjects in order to prevent excessive hemoconcentration.

When normal subjects were overly hydrated with excess salt and desoxycorticosterone acetate, the interstitial fluid took up relatively large amounts of water. As a result the plasma volume gain averaged only 12 per cent of the increase in total extracellular (thiocyanate) space although the absolute increase in plasma volume was similar in amount to the reduction occurring during dehydration of normal subjects. The intracellular fluid volume appeared to decrease during this period, with an average shift of almost 2 L. of fluid from the intracellular to the extracellular space. A similar fluid shift following desoxycorticosterone acetate has been noted previously by Loeb and his associates¹² in a patient with Addison's disease. Also a slight decrease in the intracellular water of muscle tissue after desoxycorticosterone acetate administration has been observed in dogs by Harkness and his associates.⁶ In addition, they noted considerable replacement of intracellular potassium with sodium. It should be noted that the apparent decrease in intracellular fluid space presumes that the distribution of thiocyanate is the same after as compared to before DCA. However, it is possible that the thiocyanate ion may penetrate cells to a greater extent after DCA, due to possible changes in cellular permeability produced by the drug, with the result that the shift of fluid from the cells to the interstitial compartment would be more apparent than real.

Following the injection of mercurhydrin, there appeared to be a specific reversal of this DCA effect, with a return of plasma volume, thiocyanate space and body

weight to approximate pretreatment values. These changes toward normal indicated an apparent shift back into the intracellular space of the fluid previously lost to the extracellular compartment.

Although the plasma volume and intracellular fluid space appeared to fluctuate in both normal and edematous patients with changes in hydration, the absolute amount of change in these fluid compartments appeared to be relatively constant under the varied conditions of these experiments. The mean decrease in plasma volume with dehydration in normal subjects agrees closely with the plasma volume reductions observed by Lyons, Avery and Jacobson¹ in a similar experiment while the mean increase in plasma volume in overly hydrated patients is in good agreement with the increases of plasma volume observed by Clinton and Thorn⁴ who also produced excessive hydration in normal individuals with DCA. While such uniformity may be fortuitous, it suggests that relatively constant fractions of the plasma volume and possibly the intracellular fluid space are able to shift during changes in hydration. It is possible that greater changes in plasma and intracellular fluid volume would occur only under more drastic conditions than those induced during these studies.²

However, the interstitial fluid space appeared to take up relatively large amounts of fluid, and once having taken up an excess appeared to contribute a larger share to the diuresis resulting from dehydrating procedures. Thus beyond certain limits the interstitial fluid space appeared to "spare" the plasma and intracellular fluid volumes. This relatively great capacity of the interstitial fluid space was not apparent, however, in the dehydrated normal patients. Although the degree of dehydration was not excessive in these experiments, the fact that clinically the hematocrit may rise to high values during dehydration suggests that the ability of the interstitial fluid space to spare plasma volume is not as great during severe dehydration as it is during excessive hydration.

The changes in the hematocrit value and plasma protein concentration reflected qualitatively rather than quantitatively the fluctuations in plasma volume and would seem to have value clinically only as rough guides to the directional changes in plasma volume. Since in the absence of hemorrhage the red cell volume is relatively stable, it appeared somewhat surprising that the hematocrit change should be less accurate a measure of plasma volume shifts than the change in plasma protein concentration. However, since the hematocrit value differs in the small as contrasted to the large vessels,¹³ the venous blood samples do not measure accurately the total body hematocrit. Further, it is possible that some redistribution of the fluid and cellular elements of the blood may occur under conditions of changing body hydration.

SUMMARY AND CONCLUSIONS

Determinations of plasma volume (T-1824), thiocyanate space, body weight, hematocrit value and plasma protein concentration carried out before and after hydrating and dehydrating procedures in man revealed that:

1. During acute dehydration produced by salt and fluid restriction plus ammonium chloride and mercupurin in four normal subjects the plasma volume and interstitial fluid space each contributed approximately 25 per cent of the total weight loss. By inference the intracellular fluid apparently contributed 50 per cent of the loss.

2. During similarly induced dehydration in four edematous patients the interstitial fluid compartment contributed approximately 85 per cent, the plasma volume approximately 5 per cent and the intracellular fluid space 10 per cent of the body water loss.

3. The greater percentage loss of total extracellular fluid in the edematous as contrasted with the normal subjects was due to the greater absolute amount lost from the interstitial fluid space in the edematous patients. The absolute loss of plasma and intracellular fluid volumes

was essentially similar in the edematous and normal individuals.

4. During excessive hydration of four normal subjects with salt and desoxycorticosterone acetate there was a proportionately great increase in interstitial fluid volume, a proportionately less increase in plasma volume and an apparent shift of fluid from the intracellular to the extracellular compartment. Mercuhydrin appeared to reverse this abnormal distribution of body water after DCA.

5. The absolute amounts of gain or loss from the plasma volume and the calculated intracellular fluid space were relatively constant under the conditions of these experiments, the proportionate differences being accounted for by the lability of the interstitial fluid space.

6. The per cent changes in hematocrit value and plasma protein concentration during these studies indicated qualitatively but not quantitatively the per cent changes in plasma volume.

REFERENCES

1. LYONS, R. H., AVERY, N. L. and JACOBSON, S. D. Effect of dehydration produced by mercupurin, on the plasma volume of normal persons. *Am. Heart J.*, 28: 247-255, 1944.
2. MELLORS, R. C., MUNTWYLER, E., MAUTZ, F. R. and ABBOT, W. E. Changes of the plasma volume and "available (thiocyanate) fluid" in experimental dehydration. *J. Biol. Chem.*, 144: 785-793, 1942.
3. HAPPER, J., ELKINGTON, J. R. and WINKLER, A. W. Plasma volume of dogs in dehydration with and without salt loss. *J. Clin. Investigation*, 23: 111-117, 1944.
4. CLINTON, M. and THORN, G. W. Effect of desoxycorticosterone acetate administration on plasma volume and electrolyte balance of normal human subjects. *Bull. Johns Hopkins Hosp.*, 72: 255-264, 1942-1943.
5. DECHERD, G. M., CALVIN, D. B. and HERRMANN, G. R. Blood plasma volume and serum protein studies during diuresis. *Texas Rep. Biol. & Med.*, 2: 47-60, 1944.
6. HARKNESS, D. M., MUNTWYLER, E., MAUTZ, F. R. and MELLORS, R. C. Electrolyte and water exchange between skeletal muscle "available (thiocyanate) fluid," and plasma in the dog following the administration of desoxycorticosterone acetate. *J. Lab. & Clin. Med.*, 28: 307-313, 1942-1943.
7. DARROW, D. C. Body-fluid physiology: the relation of tissue composition to problems of water and electrolyte balance. *New England J. Med.*, 233: 91-97, 1945.

8. GAMBLE, J. L. Chemical anatomy, physiology and pathology of extracellular fluid—a lecture syllabus. Department of pediatrics, Harvard Medical School, 1939.
9. FREIS, E. D. and SMITHWICK, R. H. The effect of lumbodorsal splanchnicectomy on the blood volume and “thiocyanate space” of patients with essential hypertension. *Am. J. M. Sc.*, 214: 363–367, 1947.
10. KALTREIDER, N. L., MENEELY, G. R., ALLEN, J. R. and BALE, W. F. Determination of the volume of extracellular fluid of the body with radioactive sodium. *J. Exper. Med.*, 74: 569, 1941.
11. LYONS, R. H., SANDERS, J. and JOHNSTON, F. D. Changes in the circulation with small changes in body fluid. *Univ. Hosp. Bull., Ann Arbor*, 11: 10–12, 1945.
12. LOEB, R. F., ATCHLEY, D. W., FERREBEE, J. W. and RAGAN, C. Observations on effect of desoxycorticosterone esters and progesterone in patients with Addison's disease. *Tr. A. Am. Physicians*, 54: 285–296, 1939.
13. GIBSON, J. G., II, PEACOCK, W. C., SELIGMAN, A. M. and SACK, T. Circulating red cell volume measured simultaneously by the radioactive iron and dye methods. *J. Clin. Investigation*, 25: 838, 1946.

Insulin Mixtures*

Experiences in the Use of Extemporaneous Bottle Mixtures in Diabetic Clinic Patients

BERT H. WIESEL, M.D., A. BANKSTON RISER, M.D. and STANLEY S. KAHN, M.D.†
Birmingham, Alabama

THE principle of prolonged action has been the basis of a number of refinements in the management of diabetes mellitus since the introduction of protamine zinc insulin in 1935. The latent period after injection soon proved to be the major defect in the mechanics of this insulin although it is of no importance in the milder cases requiring up to 40 units of insulin daily to produce a normal fasting blood sugar. In the severer diabetics there is either a postprandial hyperglycemia, particularly after breakfast, or frequent early morning hypoglycemia when the insulin dosage is increased to avoid this. These diabetics must then be given additional unmodified insulin for its immediate effect, as well as protamine zinc insulin which controls the morning blood sugar. Satisfactory control for a number of diabetics could be achieved only by two or more injections of insulin daily with greater care being required to avoid untoward side effects.

Attempts to develop a preparation with the depot action of protamine zinc insulin combined with the immediate effect of unmodified insulin were the logical result. Several reports on the injections of the two insulins in combination appeared, but it was not until 1941 that Ulrich¹ pointed out that thorough mixing was necessary to achieve predictable results. He found that the excess protamine was utilized to produce more long-acting insulin and that less than one part of regular insulin to one

part protamine produced no change in action of the mixture. Equal parts or more of unmodified insulin resulted in a preparation with characteristics of both types, and he showed that a 3:2 mixture controlled postprandial glycosuria. This most promising innovation was investigated in more detail by a number of other workers, and the time-activity and approximate proportionate insulin contents of different mixtures were worked out.²⁻⁶ Other modifications have been investigated,^{7,8} but extemporaneous mixtures modified to fit the needs of the individual patient seem to have the most established usefulness.⁹⁻¹⁷

The routine of management of diabetes mellitus in the Diabetic Clinic of the Medical College of Alabama must be gauged to the low educational and economic level of the clinic population. Until 1944 severe diabetics were treated with large doses of protamine zinc insulin and a postprandial spill was tolerated. Very few of the patients were capable of following a regimen of rigid diet and multiple doses of unmodified insulin with a single dose of protamine zinc insulin. Despite simplification of diet and a minimum of insulin injections, cooperation was poor and episodes of acidosis and insulin reactions were far too frequent. In 1944 a cautious trial of insulin mixtures was begun in those patients presenting the greatest problems in control. It was found almost at the outset that mixing of the insulins in a syringe as

* From the Diabetic Clinic, Department of Medicine, The Medical College of Alabama, A Division of The University of Alabama, Birmingham, Ala.

† Presently at Department of Nutrition, Harvard School of Public Health, Boston, Mass.

described in all of the published reports at that time was too complex a procedure in this type of individual. For this reason the first patients were hospitalized and given standardized mixtures prepared in the syringe in this manner. They were then

TABLE I
GUIDE FOR MIXING INSULIN

Mixture	Bottles Prescribed		Insulin Per Bottle		Excess		Final Amount of Mixture
	Regu-lar	PZ1	Regu-lar	PZ1	Regular	PZI	
1:1	1	1	5 cc	5 cc	0	0	20 cc
3:2	2	1	6 cc	4 cc	+2 cc	-2 cc	30 cc
2:1	2	1	6 5 cc	3 5 cc	+0 5 cc	-0 5 cc	30 cc
7:3	2	1	7 cc	3 cc	-1 cc	+1 cc	30 cc
3:1	2	1	7 5 cc	2 5 cc	-2 5 cc	+2 5 cc	30 cc

changed over to a mixture of the same proportion prepared in a bottle. Mixtures prepared in amounts up to 1,600 units at one time gave no clinical results appreciably different from that expected of those prepared in the syringe, and after some experience patients were changed directly from protamine zinc insulin or a combination of insulins to a premixed preparation. During the course of this study a report appeared which confirms our finding that after the original changes occur in mixing the insulin no further alteration in action is apparent due to the time elapsing before the insulin is used.¹⁷

All patients on insulin mixtures were given one of the standard clinic diets. These consist of moderately high carbohydrate allowances in the following proportions:

1,280 calories, 120 Gm. CHO
1,510 calories, 150 Gm. CHO
1,750 calories, 165 Gm. CHO
1,900 calories, 180 Gm. CHO
2,000 calories, 200 Gm. CHO

The diet outline is presented in household measures, and each patient keeps a notebook which is checked by the dietitian at every clinic visit. Additions or subtractions are made to these standard diets as excess weight or physical activity may indicate.

Fasting blood sugar and urinalysis are obtained at each visit, and a blood sugar level of 90 to 130 mg. per cent is taken to indicate satisfactory control. The insulin prescription is prepared and the clinic nurse mixes the insulin for the patient

TABLE II
252 CONSECUTIVE REGISTRATIONS OF DIABETIC CLINIC PATIENTS

	No of Cases	% of Total	Sex		Race		Mean Age
			Male	Fe-male	White	Col ored	
Diet alone	33	13	3	30	7	26	51
PZ1 only	151	60	40	111	55	96	53 4
PZ1 plus regular	1	0 4	1	0	1	0	65
Mixtures	67	26 6	25	42	32	35	36 5
Totals	252		69	183	95	157	48 7

during the visit in amounts calculated to last until the next appointed visit.

All precautions are taken to avoid contamination. Sterile empty insulin bottles are available to facilitate mixing without excessive transferring of the material. The nurse responsible for mixing the insulin is guided by a chart which has been prepared for this purpose. (Table 1.) Care is taken that the syringes are freshly sterilized and the bottle tops are thoroughly cleansed with alcohol. The proper amount of insulin is withdrawn from a new vial containing 10 cc. The other type insulin is then added as indicated, care being taken first to withdraw the proper amount of air so that excessive foaming does not occur. Excess insulin which results is kept and used to make up a deficit in a later mixing. One or two extra vials of insulin ensure the prevention of any waste at all.

Twenty-four-hour urine specimens are not obtained but in some cases it has been possible to have the patient record urinalyses for sugar three times daily. If a patient suffers from numerous reactions or if there is persistent hyperglycemia, hospitalization is instituted.

An analysis of 252 consecutive clinic registrations is presented in Table II. The thirty-three patients controlled on diet

alone represent 13 per cent of the group with a mean age of fifty-one years. Protamine zinc insulin given as one injection in the morning before breakfast is employed in 151 cases or 60 per cent of the total, the mean age being 53.4 years. Only one

insulin in proportion to protamine. Other ratios are used much less frequently, but any proportion may be mixed to suit the demands of the individual patient.

There has been no attempt to obtain a control group by keeping a part of the group on protamine and supplementary unmodified insulin, mainly because of the previous difficulties encountered in this method of treatment. It is possible to compare the behavior of patients with records of several years of treatment prior to being placed on bottle mixtures. Three cases representative of satisfactory results are briefly presented:

TABLE III

ANALYSIS OF PATIENTS ON INSULIN MIXTURES

Mixture	Total No.	% of Total	Male	Female	White	Colored	Mean Age	Mean Dosage
1:1	28	41.8	10	18	17	11	34.9	59.7
3:2	1	1.5	1	0	0	1	30	65
2:1	27	40.3	10	17	15	12	37.7	69.9
7:3	7	10.4	3	4	0	7	39.8	68
3:1	4	6.0	1	3	0	4	35.2	62.5
Total	67	25	42	32	35	36.5	64.9

patient received supplementary unmodified insulin injections in addition to depot insulin. The patients with the more severe cases that in the past have had to have such treatment are included in the group of sixty-seven patients given insulin mixtures. This represents 26.6 per cent of the patients with a mean age of 36.5 years. The marked difference in the mean age of those on mixtures as compared with those on protamine alone or diet is illustrative of the younger, more severe diabetics requiring the mixture. The clinic population as a whole is pictured in this tabulation. The greater proportion of colored to white patients illustrates the composition of the clinic population of a southern charity out-patient department.

Table III presents an analysis of the sixty-seven patients receiving mixtures, all using premixed bottle mixtures. The greatest group, twenty-eight cases or 41.8 per cent, are on a 1:1 mixture with a mean dosage of 59.7 units. The next largest group is that given two parts of unmodified insulin to one part of protamine zinc. There were twenty-seven patients on this 2:1 mixture representing 40.3 per cent with a mean dosage of 69.9 units. This difference in total dosage is probably significant and is in keeping with the experience of others who find that the greater the total dosage, the greater the requirement of unmodified

CASE REPORTS

CASE I. H. T., aged twenty-two, was a negro male. This patient was admitted October 15, 1942, at which time diabetes was diagnosed. He was discharged after being given 60 units of protamine zinc insulin. On October 16, 1943, he was re-admitted in diabetic acidosis. Fifty units of protamine zinc insulin was the dose on discharge. Control remained generally unsatisfactory and on July 10, 1947, he was re-admitted for standardization and discharged on 65 units of a 2:1 mixture. He has required no admission since this date and control has been more satisfactory.

CASE II. S. I., aged forty-four, was a negro male. Diabetes was diagnosed elsewhere in 1924 or 1925, and he was first seen in the clinic on July 24, 1945. He was placed on 80 units of protamine zinc insulin daily and remained on this dosage until March 29, 1946, during which time his blood sugar ranged from 96 to 310 mg. per cent. He was then placed on 65 units of a 7:3 mixture which was gradually decreased to 45 units. His blood sugars have ranged from 60 to 180 mg. per cent with one exception; there have been no severe reactions or hospital admissions.

CASE III. E. M. B., aged eighteen, was a negro female. Diabetes was diagnosed in 1935, and treatment with insulin was begun elsewhere in 1936. She was first seen in the clinic on March 20, 1945, and given 40 units of protamine zinc insulin twice daily. On September 6, 1945, she was admitted in mild acidosis. She was placed on a 2:1 mixture on September 20th and was discharged using 90 units of a 2:1

mixture. On October 18, 1945, she was changed to a 7:3 mixture. She was re-admitted to the hospital on December 29, 1945, in acidosis accompanying acute tonsillitis. Upon discharge she was given a 1:1 mixture, 90 units in divided doses, morning and evening. In June, 1947, elective tonsillectomy was performed, and she was discharged taking 100 units of a 2:1 mixture given in one daily morning dose. She did so well that she lapsed in her clinic visits after December, 1947, and was not seen again until April 14, 1948, when she was admitted to the hospital with polyarthritis, hypertension and mild acidosis. Since her discharge, she has been well regulated on a dosage of 95 units of a 2:1 mixture.

Some of the patients show poor control on mixtures but often there is complete disregard of diet and irresponsibility in reporting complications. The fourth case is presented as an example of this type:

CASE IV. L. C., aged sixteen, was a white female. Diabetes was diagnosed at the age of four. She was first treated in the clinic in July, 1945, and given protamine zinc insulin. Hospital admissions were necessary in September, 1945 for diabetic leg ulcers and in August, 1946, for impetigo. After the second admission she was discharged on 90 units of a 2:1 mixture. On November 9, 1946, the dosage was changed to 65 units of a 3:1 mixture with no improvement in control. On April 7, 1947, she was admitted in acidosis and precoma accompanied by acute pharyngitis. Upon recovery she was discharged on 90 units of a 3:2 mixture. A fourth admission occasioned by acidosis occurred in June, 1947, and she was discharged on 80 units of a 2:1 mixture. On July 2, 1947, she was admitted with an abscess of the right thigh, apparently due to use of an unsterile insulin syringe. Culture of the insulin revealed no organisms to be present. On September 15th she was again admitted with an abscess of the thigh, and after incision and drainage she was discharged using 75 units of a 2:1 mixture. There have been no subsequent admissions, but control has been poor on 75 to 80 units of a 2:1 mixture, the blood sugar ranging from 58 to 263 mg. per cent.

In addition to poor control due to improper cooperation, Case IV represents one of two instances of abscess formation that

have occurred in patients receiving premixed insulin. The possibility of contamination in mixing the insulins was seriously considered at the outset, but it was believed that there was less chance of infection in mixing the insulins under ideal conditions in the clinic than there would be in allowing these patients to take multiple injections at home or to attempt to mix the insulins in the syringe. Despite the mixing of from two to four vials of insulin at one time, the unsterile syringe remains the greatest hazard insofar as infections are concerned.

SUMMARY AND CONCLUSIONS

An analysis of 252 diabetic clinic patients is presented, sixty-seven of whom have been under treatment with insulin mixtures.

Insulin mixtures have a place in the management of severe diabetics, juvenile diabetics and moderately severe adult diabetics. The necessity of multiple injections is avoided, and control is more satisfactory than with one injection of protamine zinc insulin and supplementary injections of unmodified insulin.

Insulin mixtures may be premixed in the desired proportion in the bottle with no change in action apparent clinically and with little danger of infection.

REFERENCES

1. ULRICH, H. Clinical experiments with mixtures of standard and protamine zinc insulins. *Ann. Int. Med.*, 14: 1166-1179, 1941.
2. PECK, F. B. Action of insulins. *Proc. Am. Diabetes A.*, 2: 69-83, 1942.
3. PECK, F. B. Approximate insulin content of extemporaneous mixtures of insulin and protamine zinc insulin. *Ann. Int. Med.*, 18: 177-181, 1943.
4. COLWELL, A. R. and IZZO, J. L. Protamine zinc insulin modified for accelerated action. *J. A. M. A.*, 122: 1231-1236, 1943.
5. PECK, F. B. and SCHECTER, JOHN S. The newer insulin mixtures; a follow-up study. *Proc. Am. Diabetes A.*, 4: 59-86, 1944.
6. COLWELL, ARTHUR. Nature and time action of modifications of protamine zinc insulin. *Arch. Int. Med.*, 74: 331-345, 1944.
7. MACBRYDE, C. M. and ROBERTS, H. K. A new modified protamine zinc insulin: comparison with histone zinc insulin, clear and standard protamine zinc insulins. *J. Clin. Investigation*, 22: 791-797, 1943.

8. MACBRYDE, C. M. and REISS, R. S. Modified protamine zinc insulin: comparison with globin zinc insulin and insulin mixtures. *J. Clin. Endocrinol.*, 4: 469-479, 1944.
9. ADLERSBERG, D. and DOLGER, H. Insulin mixtures in the treatment of diabetes. *J. A. M. A.*, 128: 414-419, 1945.
10. CAMPOS, C. A. and RAFFAELLE, J. F. The treatment of diabetes with special reference to mixtures of insulin. *Medicina, Buenos Aires*, 6: 128-142, 1945.
11. RICKETTS, H. T. Certain aspects of the newer insulins. *Illinois M. J.*, 87: 133-136, 1945.
12. PECK, F. B. Insulin mixtures and modifications. *M. Clin. North America*, pp. 343-357, March, 1947
13. PALMER, L. J. and CRAMPTON, J. H. Experiences with insulin mixtures. *Am. J. Med.*, 3: 167-170, 1947.
14. SPRAGUE, R. G. The use of various kinds of insulin. *M. Clin. North America*, pp. 933-944, July, 1946.
15. COLLENS, W. S., BOAS, L. and ZILINSKY, J. D. Insulin mixtures: an evaluation of their use in 150 cases. *Am. J. Med.*, 3: 155-166, 1947.
16. COLWELL, ARTHUR. Effective insulin timing in diabetes mellitus. *M. Clin. North America*, pp. 327-341, March, 1947.
17. PALMER, LESTER J. Insulin in the treatment of diabetes mellitus. *J. A. M. A.*, 132: 502-507, 1946.

Cardiac Complications of Diabetes Mellitus*

IRVING M. LIEBOW, M.D. and HERMAN K. HELLERSTEIN, M.D.

Cleveland, Ohio

DIABETES mellitus is a metabolic disease. Even if the abnormal metabolism remains well controlled, however, the complications of the chronic disease are frequent, widespread and often permanent. Among the most common of these complications is heart disease. The heart is also involved occasionally when control of the disease is temporarily out of hand. Such lack of control may be in the nature of acute undertreatment (acidosis) or accidental overtreatment (hypoglycemia), and each of these states may give rise to cardiac complications. This paper is a summary of these cardiac complications of diabetes mellitus.

COMPLICATIONS OF THE CHRONIC DISEASE

Coronary Artery Sclerosis. It has been generally accepted that the incidence of arteriosclerosis is greater among diabetics than among non-diabetics. With the development since 1912 of the clinical entity of coronary occlusion and resultant myocardial infarction and with the increased interest in diabetes since the introduction of insulin ten years later, much attention has been paid to the relation of diabetes mellitus to coronary sclerosis specifically. For references to early articles on the subject the reader is referred to the bibliographies in articles by Blotner¹ and Root and Sharkey.² Subsequent articles on the subject are summarized in Table 1. It is evident from this table that there is a greater incidence of coronary arteriosclerosis in diabetics than in non-diabetics.

One of the striking aspects of this increased occurrence of coronary arteriosclerosis

among diabetics is the sex incidence. In the general population the male sex is more often affected, the ratio generally being accepted as 3 or 4 to 1.⁹⁻¹¹ In the diabetic group, however, there is a marked increase in the incidence of coronary sclerosis among females and the ratio therefore decreases. All authors are in agreement on this point although they may differ as to the degree of change. Blotner¹ reported that of thirty-four diabetics with coronary sclerosis twenty-two were female, a ratio of males to females of 1:1.8. This represents a complete reversal of the figures among normals. In a study of coronary disease in non-diabetics Nathanson³ found a ratio of 3:1 but in a similar study of diabetics⁴ the incidence dropped to 1.8:1. Hart and Lisa¹² investigated specifically the sex factor in arteriosclerosis of diabetics. Moderate and severe coronary involvement of persons over forty years of age in a large control group showed a ratio of males to females of 1.11:1; in the diabetic group this fell to 1:1.04.

There has been evidence that the occurrence of arteriosclerosis in diabetics is related to the duration of the disease and not necessarily to the age of the patient. Warren¹³ reports that in 484 autopsies on diabetics whose disease had lasted five years or more he has seen only four cases which were free from arteriosclerosis. Arteriosclerosis was present in all the others regardless of age. Shepardson¹⁴ studied the effect of diabetes of five or more years' duration in a group under forty years of age (fifty cases) and found roentgen evidence of peripheral arteriosclerosis in 36 per cent. Rabinowitch, Ritchie and McKee¹⁵ found that among

* From the Department of Medicine, Western Reserve University and the Lakeside Hospital, Cleveland, Ohio.
Read before the Cleveland Diabetes Society, January 17, 1949.

diabetics under fifty years of age who had diabetes five years or more cardiovascular disease in general occurred in 85.1 per cent. In a study of 200 diabetics below fifty years of age followed for twenty-five years, Dolger¹⁶ found that every patient developed vascular

stances. This figure of 2 per cent is higher than the incidence of diabetes in the general population. Root, Bland, Gordon and White⁵ found significant coronary sclerosis (narrowing or occlusion) in 9 per cent of diabetics under the age of forty and in only

TABLE I
CORONARY ARTERIOSCLEROSIS—OCCURRENCE IN POSTMORTEM STUDIES

Author	Degree of Sclerosis	Age Group	Non-diabetics		Diabetics	
			No. of Cases Studied	Incidence of Coronary Sclerosis Per cent	Incidence of Coronary Sclerosis Per cent	No. of Cases Studied
Blotner ¹	Well marked	Controls: 40-80 Diabetics: 13-85	450	21	45	77
Nathanson ⁴	Marked	Over 50 yr.	249	8.2	52.7	74
Root and Sharkey ²	Occlusive	40 and over	170	13	46.7	157
Root, Bland, Gordon and White ⁵	Narrowing with or without occlusion	40 and over	2,310	29	56	316
Lisa, Magiday, Galloway and Hart ⁶	Severe	40 and over	2,250	29	46	193
Stearns, Schlesinger and Rudy ⁷	Narrowing with occlusion or myocardial fibrosis	Over 40	400	37	74	50
Millard and Root ⁸	Occlusion or marked narrowing	2,310	29	68	106

damage regardless of the degree of severity of the disease, insulin requirement, type of diet or degree of control. Chute¹⁷ also reports a high incidence of vascular disease in juvenile diabetics. In view of these findings one would expect a higher incidence of coronary sclerosis in young diabetics than in non-diabetics of comparable age. Unfortunately statistics on coronary arteriosclerosis, specifically, are relatively meager for young diabetics but the available figures generally coincide with the expected. Glendy, Levine and White¹⁸ collected 100 cases of coronary disease in people under forty and found that diabetes was present in two in-

1.3 per cent of non-diabetics in the same age group. Master, Dack and Jaffe¹⁹ analyzed 500 consecutive cases of myocardial infarction. From this study they concluded that diabetes is not a factor in the occurrence of coronary occlusion in the young but nevertheless of their thirty-nine cases under the age of forty two had diabetes, an incidence of 5.1 per cent. Millard and Root⁸ report twelve young diabetics who died before the age of thirty-three. Of these five had had diabetes six years or less and showed no arteriosclerosis. Seven had had diabetes fourteen to twenty-one years and all had coronary arteriosclerosis; three had actual

coronary occlusion. These are apparently the same group reported by Root²⁰ in a separate communication.

Coronary arteriosclerosis is of significance mainly as a cause of clinical heart disease. The increased incidence of coronary sclero-

group would naturally have a higher occurrence of angina pectoris than the general population and the figure of 11.8 per cent serves to lend significance to a 9 per cent incidence of this disability among diabetics.

Angina pectoris ordinarily occurs in

TABLE 11
CORONARY THROMBOSIS—OCCURRENCE IN POSTMORTEM STUDIES

Author	Age of Group Studied	Non-diabetics		Diabetics	
		No. of Cases Studied	Incidence of Coronary Thrombosis Per cent	Incidence of Coronary Thrombosis Per cent	No of Cases Studied
Enklewitz ²⁴ . . .	50-69	520	16	31	74
Root and Sharkey ² . .	40 and over	170	2	19.6	157
Root, Bland, Gordon and White ⁵	40 and over	2,310	8	35	316
Lisa, Magiday, Galloway and Hart ⁶	40 and over	2,250	22	30	193
Stearns, Schlesinger and Rudy ⁷ .	Over 40	400	23	64	50

sis among diabetics in general, among female diabetics in particular and in the younger age groups has been shown above. It is to be expected then that in all these groups there would be a greater occurrence of the clinical results of coronary sclerosis, namely, angina pectoris, coronary thrombosis and congestive failure.

Angina Pectoris. The reported incidence of angina pectoris among diabetics shows a wide range but nevertheless most reviews are surprisingly consistent. Rabinowitch, Ritchie and McKee¹⁵ found the disability in 1.3 per cent of diabetics in an out-patient clinic while Stearns, Schlesinger and Rudy⁷ reported its occurrence in 28 per cent of necropsied diabetics as opposed to 15 per cent in their control group. Blotner,¹ Friedman²¹ and Root and Sharkey,² however, all report an incidence of 9 per cent. The author has been unable to find any statistics on the incidence of angina pectoris in the general population for purposes of comparison. The incidence parallels the occurrence of coronary artery disease and according to White¹¹ angina occurred in 11.8 per cent of a series of 3,000 patients with cardiac symptoms or signs. Such a

males and females in a ratio of 3 or 4 to 1.^{10,11} Among diabetics, however, the incidence among females increases and the ratio falls. Root and Graybiel²² found the ratio to be only 1.4:1 among diabetics. Stearns et al.⁷ found an incidence of 3.7:1 in their control group and 1:1 among the diabetics. Edeiken²³ who studied out-patients also reports a sex ratio of 1:1.

Other facts stand out as significant. Root and Graybiel²² report that of those people with angina pectoris the prognosis is worse among diabetics. In the diabetic group which they studied the duration of life from the first anginal attack was two years as opposed to White's unselected cases in which the duration was 3.4 years. Root and Sharkey² also point out that the incidence of angina pectoris trebles during the second decade of diabetes.

Coronary Thrombosis. The increased incidence of coronary thrombosis among diabetics is most marked. The papers on this subject are summarized in Table II.

Of further significance are the following facts: Not only is the incidence of coronary thrombosis increased in diabetics but the mortality following the accident is also in-

creased.¹⁹ In addition, Stearns, Schlesinger and Rudy⁷ report that in their series of necropsied diabetics one out of every three had died of acute coronary disease.

The change in sex ratio is also marked. As with coronary sclerosis, coronary thrombosis in unselected cases is three to four times as frequent in males as in females.¹⁹ Among diabetics, however, the ratio falls. In the series of Root and co-authors⁵ the incidence of coronary occlusion in male and female diabetics fifty-one to eighty years of age was equal. Stearns et al.,⁷ using Schlesinger's injection technic, found coronary occlusion in 31 per cent of male non-diabetics and in 8 per cent of females; in the diabetics it occurred in 68 per cent of men and 61 per cent of women. In other words, in their series coronary occlusion in non-diabetics was four times as frequent in men as in women but among diabetics coronary occlusion increased two-fold in men and eight-fold in women, the incidence in both sexes becoming equal.

Detailed information on angina pectoris in the young is found wanting. More information on coronary occlusion in the young is now becoming available^{19,20,25-30,92} but the number of cases reported, exclusive of studies of the armed forces (in whom diabetes is not a factor), is small. Since known diabetes occurs in less than 1 per cent of the population, few statistics are available on coronary occlusion in the young diabetic. The available figures, however, point generally to an increased incidence of coronary thrombosis. Of Durant's³⁰ seven cases of coronary thrombosis in people thirty-five years of age or less one was diabetic. Master et al.¹⁹ report thirty-nine cases of coronary thrombosis in patients under forty years of age; two (5.1 per cent) had diabetes. Among Stryker's²⁶ nine infants and children under the age of seventeen who had coronary occlusion none were diabetics. Goodson and Willis⁹² make no mention of diabetes in their report of thirty cases of coronary thrombosis in persons less than forty years of age. If all the above mentioned series are totalled (85), however, the incidence of dia-

betics (3) among them is higher than that in the general population.

Congestive Failure. There have been few reports on the incidence of congestive failure among diabetics. This is readily understandable when it is realized that congestive failure may result from any one of several causes, one or more of which may be present in a single diabetic at the same time. Coronary sclerosis alone, coronary thrombosis with myocardial infarction and hypertension may each give rise to heart failure and are frequently present in diabetics. The incidence in diabetics of the specific etiologies has interested investigators more than the occasionally resulting clinical picture of cardiac insufficiency. Root and Sharkey² merely state that in their post-mortem study congestive heart failure was infrequent; when it occurred, it usually followed coronary thrombosis. This is in contrast to other available figures. Friedman²¹ found cardiac decompensation in 8 per cent of 120 living diabetics, and Stearns et al.,⁷ reviewing the protocols of fifty necropsied diabetics, found that congestive failure had been present in twenty-seven, an incidence of 58 per cent.

CAUSES OF CORONARY ARTERIOSCLEROSIS IN DIABETES

The etiology of the increased incidence of coronary arteriosclerosis among diabetics is unknown. It is believed by some that diabetes is simply another clinical manifestation of arteriosclerosis and that an increased occurrence of arteriosclerosis anywhere in the body is to be expected. The weight of statistical evidence, however, points to the increase in arteriosclerosis in diabetics as the result rather than the cause of the disease. Two factors have been implicated as at least contributing to the increased incidence, hypertension and hypercholesterolemia.

Hypertension. References to early discussions of the blood pressure in diabetes are contained in Major's³¹ article. Opinion was divided as to whether or not diabetics showed an increased incidence of hypertension. According to Major the blood

pressure was only slightly higher in diabetics than in control series but was definitely higher in diabetic women in the older age groups. Edeiken²³ reported hypertension in 38 per cent of 100 diabetics studied clinically, the women being affected twice as often as the men. All those with high blood pressure were over fifty years of age. Bell and Clawson³² found hypertension relatively uncommon in necropsied diabetics under forty years of age but in persons over the age of fifty high blood pressure was 2.7 times as frequent in diabetics as in non-diabetics. Among the older diabetics hypertension occurred in 42.5 per cent, which is very close to the figure of 44 per cent found by Enklewitz²⁴ in his postmortem study. Other reports show an even higher incidence. Transient and permanent high blood pressure occurred in 56 per cent of Friedman's²¹ clinical series and in 53 per cent in Root and Sharkey's postmortem study.³³ Even more startling is White and Waskow's³⁴ finding of hypertension in 40 per cent of 200 diabetics, 5 per cent of whom were under forty years of age. Of recent investigations only Nathanson⁴ has found a relatively low (15 per cent) incidence of hypertension in diabetics, but even this figure is higher than that found in the general population.³⁵

Associated Findings in Coronary Arteries. The increased incidence of hypertension in diabetics is reflected in the coronary arteries. In Blotner's¹ series of necropsied diabetics high blood pressure was present in 43 per cent of those with coronary arteriosclerosis. Root and Graybiel²² found it in 52 per cent of 210 diabetics with angina pectoris. According to Root and Sharkey² coronary thrombosis is three times as frequent in diabetics with hypertension as in those without. Likewise, Stearns et al.⁷ find that among diabetics angina pectoris and deaths due to acute coronary disease and congestive failure are more common in the presence of hypertension.

Hypercholesterolemia. It is beyond the scope of this review to discuss hypercholesterolemia in relation to the pathogenesis of coronary atherosclerosis. Some mention

of the clinical association is in order, however. Cholesterol has long been implicated in the causation of atherosclerosis. The substance is found in high concentration in the plaques of atherosclerosis, and atherosclerosis is found to be of high incidence in the presence of hypercholesterolemia. The inference is that a high blood level of the sterol results in high incidence of intimal sclerosis. Such an association of events does occur in rabbits,³⁶ chickens^{37,38} and dogs.³⁹ Conversely, the administration of decholesterolizing agents such as choline, methionine, potassium iodide and thyroid results in a decrease in atherosclerosis.^{40,41}

The transfer of such experimental work to humans presents problems. The blood cholesterol levels of normal man is not readily elevated by diet. The administration of a high cholesterol diet to a large group for a long period of time would be practically difficult and perhaps eventually dangerous. Investigation of the state of the coronary arteries in patients who have disease associated with hypercholesterolemia, however, yields some of the desired information. In xanthomatosis which is characterized by high blood cholesterol the incidence of coronary sclerosis is extremely high. Muller⁴² found that of seventy-six patients who had hereditary xanthomatosis sixty-eight (90 per cent) had angina pectoris and/or myocardial infarction. Engelberg and Newman⁴³ report six cases of xanthomatosis in young adults (ages thirty-one to forty-eight), all of whom had angina pectoris and/or myocardial infarcts. Similar although perhaps less direct information is obtained from the finding of higher blood cholesterol levels in cases of uncomplicated coronary sclerosis than in normals.^{29,44-46}

CARDIAC COMPLICATIONS OF DIABETIC ACIDOSIS

Cardiovascular Collapse. Coronary arteriosclerosis in the diabetic is a complication of the chronic disease. Diabetic acidosis, the "acute" disease, also has its cardiovascular complication. Even in the absence of disease of the coronary arteries diabetic acidosis

may be associated with the type of circulatory failure commonly known as shock. The high frequency and importance of this complication is attested by many authors.⁴⁷⁻⁵³ The clinical picture is familiar: tachycardia, low blood pressure, decreased pulse pressure, cold skin, depressed sensorium. Such shock often persists in the presence of levels of blood sugar, ketones and CO₂ combining power that are approaching normal. In fact, Nicholson and Branning⁵⁴ report that of twenty-two treated but fatal cases of uncomplicated diabetic acidosis there were five who had normal blood sugar and CO₂ combining power and who showed no lesions at autopsy. All died in collapse. The complication is of grave importance because of the concomitant increase in mortality. Rabinowitch, Fowler and Bensley⁴⁹ found that the mortality in their cases of diabetic acidosis was 11.5 per cent if the systolic blood pressure was 90 mm. Hg or over; it was 53.8 per cent if under 90 mm., almost five times as great. Collen⁵² reported that mortality for those with blood pressure 90 mm. or over averaged 27.6 per cent and for those under 90 mm. 75 per cent, almost three times as great. Danowski, Winkler and Peters⁵³ found that in recovered cases of diabetic acidosis the incidence of vascular collapse had been 20 per cent; in fatal cases, 85 per cent. Collen's study⁵² is of further interest. He demonstrates that the diastolic pressure shows a much closer quantitative relationship to percentage mortality than the systolic blood pressure; also, if the pulse pressure is less than 20, the mortality is 92.8 per cent. The situation may be summarized by quoting from Danowski and his co-workers⁵³ who state "... that some measure of peripheral vascular collapse is commonly found in severe diabetic acidosis and that its persistence is the usual reason for failure to recover from acidosis."

Peters, Bulger and Eisenman⁵⁶ showed that diabetic acidosis is associated with dehydration and hemoconcentration. Chang, Harrop and Schaub,⁵⁷ using the carbon monoxide method, demonstrated that the

dehydration results in a marked decrease in the circulating blood volume, the loss of volume being chiefly a decrease in plasma; the cell volume remains intact. It was subsequently shown^{50, 51, 53, 58-60} that not only is water lost in diabetic acidosis but that sodium and chloride ions are also lost in large amounts and must be quickly replaced for the prevention or treatment of circulatory collapse. Further work^{50, 53, 61} has demonstrated the need for the administration of protein in addition to electrolytes and water in the treatment of the more severe cases of shock. More recently Howarth, McMichael and Sharpey-Schafer⁶² have shown that the low blood pressure of diabetic acidosis is due to a marked decrease in total peripheral resistance; cardiac output remains normal. Their work suggests that an effective, long-lasting vasoconstrictor agent would be the medication of choice in the treatment of diabetic shock.

Hypopotassemia. Recently it has been shown that potassium, too, is of clinical importance in diabetic acidosis and that depletion of this electrolyte often has cardiac manifestations. Potassium is lost from the body in several ways. First, there is increased excretion of the substance in diuresis due to any cause⁶³ and the diuresis associated with marked glycosuria results in loss of the electrolyte in patients going into diabetic acidosis.⁵⁹ During the height of dehydration, which corresponds to the period just before treatment of the acidosis, loss of potassium is noted in the cells.^{63, 64} The serum level remains approximately normal,⁶⁴ however, and there are no signs of potassium deficiency. The second manner of potassium loss is a relative one. Treatment consists, in part, of administration of large amounts of water. If potassium is not given in conjunction with the water, the amount of electrolyte remaining in the body at the height of acidosis is much diluted by the rehydration of treatment with resulting marked fall in the concentration of serum potassium.^{64, 65} A third way in which potassium is lost is thought by some to be due to a specific effect of insulin. Several

authors^{59,66-68} have reported a fall in concentration of serum or plasma potassium following the injection of insulin. More recent work^{65,69,70} suggests that this may be related to the passage of the electrolyte into muscle or liver in association with increased glycogen formation.

As seen above, it is with treatment of acidosis that serum potassium concentration falls. It is therefore not on admission but following institution of therapy that the results of potassium deficiency become apparent in patients with diabetic acidosis. The best known cardiac manifestation of hypopotassemia is abnormality of the electrocardiogram. In the presence of low serum potassium the latter shows abnormal increase in the P-R interval, depression of the S-T segment, prolongation of Q-T (electrical systole) and low to inverted T waves. These findings have been reported in association with the hypopotassemia of periodic paralysis,^{71,72} chronic nephritis⁷³ and other causes.⁷⁴ Bellet and Dyer⁷⁵ were the first to report consistent electrocardiographic change associated with diabetic acidosis. Although the authors did not correlate the changes with potassium concentration, the changes are those of hypopotassemia and they noted that the changes occurred not during coma but twenty-four hours later (i.e., after institution of therapy and clinical improvement of the patient). Stewart, Smith and Milhorat,⁷¹ Holler⁷⁶ and Martin and Wertman⁷⁷ have correlated these changes with the low serum potassium of treated diabetic acidosis. The latter report that of all the electrocardiographic changes found only low T waves show a high correlation with low serum potassium.

Not only is there alteration of electrical conduction in the myocardium but also new foci for the origin of the stimulating impulse appear. Bellet and Dyer⁷⁵ reported temporary auricular flutter and auricular and ventricular premature beats in some of their patients. Frenkel, Groen and Willebrands⁷⁸ report the appearance of "irregular pulse" in association with low serum potassium level with reappearance of normal rhythm

following the administration of potassium. Nicholson and Branning⁵⁴ suggest that low serum potassium may be the cause of death from collapse that occurs in some patients with diabetic acidosis whose blood sugar and CO₂ combining power have become normal following usual therapy.

EFFECTS OF INSULIN

Hypoglycemia. It must be pointed out that although the administration of insulin is necessary for the treatment of many diabetics, overdosage of the hormone in these patients may result in cardiovascular complications. Hypoglycemia may cause angina pectoris,^{79,80,82,90} myocardial infarction,⁸¹ congestive failure,⁹⁴⁻⁹⁶ changes in the electrocardiogram^{81-85,90,93,96-100,103,104} and changes in rhythm.^{82,84,85,100,101} Hypoglycemia has also been associated with the appearance of other changes of the circulation such as increase or decrease in heart rate,^{55,81,82,86,93,96} increase or decrease in blood pressure,^{82,93,102} increase in venous pressure,⁸¹ increase in pulse pressure,^{84,86} the development of an abnormal heart murmur^{55,84} and increase in heart size.⁸⁴

The explanation for these changes is not yet clear. The obvious thought is that with hypoglycemia there is concomitant marked loss of myocardial glycogen and that this gives rise to the cardiac abnormalities. Cruickshank,^{87,88} however, showed that the diabetic heart has a much greater than normal glycogen content in the presence of hyperglycemia and that with the administration of insulin the glycogen content falls only to normal. Even in the presence of very low blood sugar insulin conserves the glycogen stored in the heart. Other facts also suggest that the low blood sugar alone is not the cause of the cardiovascular changes observed in hypoglycemia. There is no correlation between clinical findings and the blood sugar level;⁸³ the changes seen are not necessarily, or promptly, reversed by the administration of glucose.^{83,84,96} Probably the most tenable theory of the causation of cardiovascular changes in hypoglycemia is that the low blood sugar causes increased

discharge of adrenalin. Cannon, McIver and Bliss⁸⁹ demonstrated in cats that even the completely denervated heart responds to hypoglycemia by an increase in rate if the adrenals are intact. If the adrenals are removed or one is removed and the other denervated, insulin hypoglycemia causes no increase in rate. It is well known that the injection of adrenalin into the normal human produces many of the clinical signs of hypoglycemia (tachycardia, pallor, tremor, increased blood pressure). Furthermore Gilbert and Goldzieher⁸¹ have demonstrated that the usual circulatory changes taking place in insulin hypoglycemia do not occur if prostigmin is administered at the same time as the insulin.

Whatever the mode of causation, the danger of insulin overdosage is appreciable. Ernstene and Altschule,⁸⁶ working with normal humans, showed that insulin hypoglycemia results in increased heart rate, increased pulse pressure and increased minute volume output, i.e., cardiac work is greater. Such added work gave rise to no difficulty in their normal subjects but they suggest that among diabetics, a large percentage of whom have coronary arteriosclerosis, such added work could readily result in cardiac insufficiency and/or angina pectoris. For the same reason Gilbert and Goldzieher⁸¹ believe that close control of elderly diabetics is not desirable and Smith,⁹⁵ citing the clinical complications of the treatment of diabetes, states that “. . . to use insulin to procure exact control of the diabetes in patients with additional heart disease is to court disaster.”

Some of the effects of insulin may be bothersome even in the absence of marked hypoglycemia. It is common experience in the treatment of diabetics that many patients simply feel better with slight glycosuria than with excellent control. The cardiac symptoms (tachycardia, palpitation, substernal pain, shortness of breath) associated with spontaneous hypoglycemia are very distressing⁹¹ and such symptoms occur in diabetics with only slight insulin overdosage. It is interesting to note that

some of them (palpitation, precordial pain) have also been reported in patients who were given therapeutic amounts of insulin and who did not have hypoglycemia.⁸²

SUMMARY

1. The cardiac complications of diabetes mellitus are discussed under the following headings: (1) coronary arteriosclerosis, (2) diabetic acidosis and (3) hypoglycemia.

2. There is a higher incidence of coronary arteriosclerosis and its clinical manifestations among diabetics than among non-diabetics. This higher incidence is more marked in women. The duration of the diabetes is probably the greatest single factor in the occurrence of coronary arteriosclerosis.

3. Cardiovascular collapse occurs frequently in diabetic acidosis. Prevention and treatment of such shock consists of the administration of adequate amounts of water, sodium chloride, protein and potassium.

4. Insulin reactions are associated with cardiac complications particularly in the older age groups. Completely aglycosuric control of elderly diabetics by the use of insulin is not desirable.

REFERENCES

1. BLOTNER, H. Coronary disease in diabetes mellitus. *New England J. Med.*, 203: 709, 1930.
2. ROOT, H. F. and SHARKEY, T. P. Coronary arteriosclerosis in diabetes mellitus. *New England J. Med.*, 215: 605, 1936.
3. NATHANSON, M. H. Disease of the coronary arteries. Clinical and pathological features. *Am. J. M. Sc.*, 170: 240, 1925.
4. NATHANSON, M. H. Coronary disease in 100 autopsied diabetics. *Am. J. M. Sc.*, 183: 495, 1932.
5. ROOT, H. F., BLAND, E. F., GORDON, W. H. and WHITE, P. D. Coronary atherosclerosis in diabetes mellitus. *J. A. M. A.*, 113: 27, 1939.
6. LISA, J. R., MAGIDAY, M., GALLOWAY, I. and HART, J. F. Arteriosclerosis with diabetes mellitus. A study of the pathologic findings in 193 diabetic and 2,250 non-diabetic patients. *J. A. M. A.*, 120: 192, 1942.
7. STEARNS, S., SCHLESINGER, M. J. and RUDY, A. Incidence and clinical significance of coronary artery disease in diabetes mellitus. *Arch. Int. Med.*, 80: 463, 1947.
8. MILLARD, E. B. and ROOT, H. F. Degenerative vascular lesions and diabetes mellitus. *Am. J. Digest. Dis.*, 15: 41, 1948.
9. CLAWSON, B. J. The incidence of types of heart disease among 30,265 autopsies with special

- reference to age and sex. *Am. Heart J.*, 22: 607, 1941.
10. LEVINE, S. A. *Clinical Heart Disease*, 2nd ed., p. 93. Philadelphia and London, 1940. W. B. Saunders Co.
 11. WHITE, P. D. *Heart Disease*. 3rd ed. New York, 1944. Macmillan Company.
 12. HART, J. F. and LISA, J. R. Arteriosclerosis in diabetes. A consideration of the sex factor from anatomic findings. *Clinics*, 3: 196, 1944.
 13. WARREN, S. *The Pathology of Diabetes Mellitus*. 2nd ed. Philadelphia, 1938. Lea and Febiger.
 14. SHEPARDSON, H. CLARE. Arteriosclerosis in the young diabetic patient. *Arch. Int. Med.*, 45: 674, 1930.
 15. RABINOWITCH, I. M., RITCHIE, W. L. and McKEE, S. H. A statistical evaluation of different methods for the detection of arteriosclerosis in diabetes mellitus. *Ann. Int. Med.*, 7: 1478, 1934.
 16. DOLGER, H. The clinical evaluation of vascular damage in diabetes mellitus. *Bull. New York Acad. Med.*, 22: 482, 1946; *J. A. M. A.*, 134: 1289, 1947.
 17. CHUTE, A. L. Survey of patients with juvenile diabetes mellitus. *Am. J. Dis. Child.*, 75: 1, 1948.
 18. GLENDY, R. E., LEVINE, S. A. and WHITE, P. D. Coronary disease in youth. *J. A. M. A.*, 109: 1775, 1937.
 19. MASTER, A. M., DACK, S. and JAFFE, H. L. Age, sex and hypertension in myocardial infarction due to coronary occlusion. *Arch. Int. Med.*, 64: 767, 1939.
 20. ROOT, H. F. Diabetes and arteriosclerosis in youth. *Am. Heart J.*, 35: 860, 1948.
 21. FRIEDMAN, G. Cardiovascular status of diabetic patients after the fourth decade of life. *Arch. Int. Med.*, 55: 371, 1935.
 22. ROOT, H. F. and GRAYBIEL, A. Angina pectoris and diabetes mellitus. *J. A. M. A.*, 96: 925, 1931.
 23. EDEIKEN, J. Diabetes mellitus as observed in 100 cases for 10 or more years. II. Cardiac studies. *Am. J. M. Sc.*, 209: 8, 1945.
 24. ENKLEWITZ, M. Diabetes and coronary thrombosis. An analysis of cases which came to necropsy. *Am. Heart J.*, 9: 386, 1934.
 25. YATER, W. M., TRAUM, A., BROWN, W., FITZGERALD, R., GEISLER, M. and WILCOX, B. Coronary artery disease in men eighteen to thirty-nine years of age. *Am. Heart J.*, 36: 334, 481, 683, 1948.
 26. STRYKER, W. A. Coronary occlusive disease in infants and in children. *Am. J. Dis. Child.*, 71: 280, 1946.
 27. FRENCH, A. J. and DOCK, W. Fatal coronary arteriosclerosis in young soldiers. *J. A. M. A.*, 124: 1233, 1944.
 28. LISA, J. R. and HART, J. F. Arteriosclerosis in the young. A study of 372 autopsies with a report of 6 positive cases. *Clinics*, 3: 186, 1944.
 29. UNDERDAHL, L. D. and SMITH, H. L. Coronary artery disease in women under the age of forty. *Proc. Staff. Meet., Mayo Clin.*, 22: 479, 1947.
 30. DURANT, T. M. The occurrence of coronary thrombosis in young individuals. *Ann. Int. Med.*, 10: 979, 1937.
 31. MAJOR, G. G. Blood pressure in diabetes mellitus. *Arch. Int. Med.*, 44: 797, 1929.
 32. BELL, E. T. and CLAWSON, B. J. Primary (essential) hypertension. A study of four hundred twenty cases. *Arch. Path.*, 5: 939, 1928.
 33. ROOT, H. F. and SHARKEY, T. P. Arteriosclerosis and hypertension in diabetes. *Ann. Int. Med.*, 9: 873, 1936.
 34. WHITE, P. and WASKOW, E. Clinical pathology of diabetes in young patients. *South. M. J.*, 41: 561, 1948.
 35. CECIL, RUSSELL L. *Textbook of Medicine*. 6th ed., p. 1031. Philadelphia, 1943. W. B. Saunders Co.
 36. LEARY, T. Experimental atherosclerosis in the rabbit compared with human (coronary) atherosclerosis. *Arch. Path.*, 17: 453, 1934.
 37. DAUBER, D. V. and KATZ, L. N. Experimental cholesterol atheromatosis. In an omnivorous animal, the chick. *Arch. Path.*, 34: 937, 1942.
 38. DAUBER, D. V. and KATZ, L. N. Experimental atherosclerosis in the chick. *Arch. Path.*, 36: 473, 1943.
 39. STEINER, A. and KENDALL, F. E. Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil. *Arch. Path.*, 42: 433, 1946.
 40. HERRMANN, G. R. Experimental and clinical studies in hypercholesterolemia and atherosclerosis and the effects of decholesterolizing agents. *Am. Heart J.*, 33: 711, 1947.
 41. HORLICK, L., DAUBER, D. and KATZ, L. N. Thyroid and experimental atherosclerosis in the chicken. *Am. Heart J.*, 35: 863, 1948.
 42. MULLER, C. Angina pectoris in hereditary xanthomatosis. *Arch. Int. Med.*, 64: 675, 1939.
 43. ENGELBERG, H. and NEWMAN, B. A. Xanthomatosis. A cause of coronary artery disease in young adults. *J. A. M. A.*, 122: 1167, 1943.
 44. STEINER, A. and DOMANSKI, B. Serum cholesterol level in coronary arteriosclerosis. *Arch. Int. Med.*, 71: 397, 1943.
 45. BOAS, E. P., PARETS, A. D. and ADLERSBERG, D. Hereditary disturbance of cholesterol metabolism: a factor in the genesis of atherosclerosis. *Am. Heart J.*, 35: 611, 1948.
 46. MORRISON, L. M., HOLL, L. and CHANEY, A. L. Cholesterol metabolism: blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis. *Am. J. M. Sc.*, 216: 32, 1948.
 47. BAKER, T. W. A clinical survey of one hundred eight consecutive cases of diabetic coma. *Arch. Int. Med.*, 58: 373, 1936.
 48. DILLON, E. S. and DYER, W. W. Factors influencing the prognosis in diabetic coma. *Ann. Int. Med.*, 11: 602, 1937.
 49. RABINOWITCH, I. M., FOWLER, A. F. and BENSLEY, E. H. Diabetic coma (an investigation of mortalities and report of a severity index for comparative studies). *Ann. Int. Med.*, 12: 1403, 1939.
 50. SCHECHTER, A. E., WIESEL, B. H. and COHEN, C. Peripheral circulatory failure in diabetic acidosis and its relation to treatment. *Am. J. M. Sc.*, 202: 364, 1941.

51. BEARDWOOD, J. T., JR. and ROUSE, G. R. Diabetic acidosis. A study of 220 consecutive cases. *J. A. M. A.*, 117: 1701, 1941.
52. COLLEN, M. F. Mortality in diabetic coma. *Arch. Int. Med.*, 70: 347, 1942.
53. DANOWSKI, T. S., WINKLER, A. W. and PETERS, J. P. Salt depletion, peripheral vascular collapse, and the treatment of diabetic acidosis. *Yale J. Biol. & Med.*, 18: 405, 1946.
54. NICHOLSON, W. M. and BRANNING, W. S. Potassium deficiency in diabetic acidosis. *J. A. M. A.*, 134: 1292, 1947.
55. WIECHMANN, E. and KOCH, F. Untersuchungen über den hypoglykämischen Zustand nach Insulininjektion; das Verhalten des Kreislaufs im hypoglykämischen Zustand. *Deutsche Arch. f. klin. Med.*, 163: 176, 1929.
56. PETERS, J. P., BULGER, H. A. and EISENMAN, A. J. The plasma proteins in relation to blood hydration. II. In diabetes mellitus. *J. Clin. Investigation*, 1: 451, 1925.
57. CHANG, H. C., HARROP, G. A. JR., and SCHAUB, B. M. The circulating blood volume in diabetic acidosis. *J. Clin. Investigation*, 5: 407, 1928.
58. KYDD, D. M. Salt and water in the treatment of diabetic acidosis. *J. Clin. Investigation*, 12: 1169, 1933.
59. ATCHLEY, D. W., LOEB, R. F., RICHARDS, D. W., JR., BENEDICT, E. M. and DRISCOLL, M. E. On diabetic acidosis—a detailed study of electrolyte balances following the withdrawal and re-establishment of insulin therapy. *J. Clin. Investigation*, 12: 297, 1933.
60. ROOT, H. F. The use of insulin and abuse of glucose. *J. A. M. A.*, 127: 557, 1945.
61. PETERS, J. P., KYDD, D. M. and EISENMAN, A. J. Serum proteins in diabetic acidosis. *J. Clin. Investigation*, 12: 355, 1933.
62. HOWARTH, S. McMICHAEL, J. and SHARPEY-SCHAFER, E. P. Low blood pressure in diabetic coma. *Clin. Sci.*, 6: 247, 1948.
63. ELKINTON, J. R. and WINKLER, A. W. Transfers of intracellular potassium in experimental dehydration. *J. Clin. Investigation*, 23: 93, 1944.
64. DANOWSKI, T. S., HALD, P. M. and PETERS, J. P. Sodium, potassium and phosphates in the cells and serum of blood in diabetic acidosis. *Am. J. Physiol.*, 149: 667, 1947.
65. MARTIN, H. E. and WERTMAN, M. Electrolyte changes and the electrocardiogram in diabetic acidosis. *Am. Heart J.*, 34: 646, 1947.
66. HARROP, G. A., JR. and BENEDICT, E. M. The participation of inorganic substances in carbohydrate metabolism. *J. Biol. Chem.*, 59: 683, 1924.
67. BRIGGS, A. P., KOECHIG, I., DOISY, E. A. and WEBER, C. J. Some changes in the composition of blood due to the injection of insulin. *J. Biol. Chem.*, 58: 721, 1924.
68. KERR, S. E. The effect of insulin and of pancreatectomy on the distribution of phosphorus and potassium in the blood. *J. Biol. Chem.*, 78: 35, 1928.
69. FENN, W. O. The role of potassium in physiological processes. *Physiol. Rev.*, 20: 377, 1940.
70. KOMETIANA, P. A., GOGOLASHVILI, S. H. and DOLIDZE, S. The relation between the resynthesis of glycogen and the distribution of potassium in muscular tissue. *Diabetic Abstracts*, 7: 84, 1948.
71. STEWART, H. J., SMITH, J. J. and MILHORAT, A. T. Electrocardiographic and serum potassium changes in familial periodic paralysis. *Am. J. M. Sc.*, 199: 789, 1940.
72. STOLL, B. and NISNEWITZ, S. Electrocardiographic studies in a case of periodic paralysis. *Arch. Int. Med.*, 67: 755, 1941.
73. BROWN, M. R., CURRENS, J. H. and MARCHAND, J. F. Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis. *J. A. M. A.*, 124: 545, 1944.
74. TARAIL, R. Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances. *Am. J. Med.*, 5: 828, 1948.
75. BELLET, S. and DYER, W. W. The electrocardiogram during and after emergence from diabetic coma. *Am. Heart J.*, 13: 72, 1937.
76. HOLLER, J. W. Potassium deficiency occurring during the treatment of diabetic acidosis. *J. A. M. A.*, 131: 1186, 1946.
77. MARTIN, H. E. and WERTMAN, M. Serum potassium, magnesium and calcium levels in diabetic acidosis. *J. Clin. Investigation*, 26: 217, 1947.
78. FRENKEL, M., GOREN, J. and WILLEBRANDS, A. F. Reduction of serum potassium content with manifestations of generalized muscular weakness and a cardiovascular syndrome during treatment of diabetic coma. *Nederl. tijdschr. v. geneesk.*, 91: 1704, 1947.
79. TURNER, K. B. Insulin shock as the cause of cardiac pain. Case report. *Am. Heart J.*, 5: 671, 1930.
80. VON NOORDEN, C. Die Zuckerkrankheit und ihre Behandlung. 6th ed., p. 205. Berlin.
81. GILBERT, R. A. and GOLDZIEHER, J. W. The mechanism and prevention of cardiovascular changes due to insulin. *Ann. Int. Med.*, 25: 928, 1946.
82. SOSKIN, S., KATZ, L. N., STROUSE, S. and RUBINFELD, S. H. Treatment of elderly diabetic patients with cardiovascular disease. *Arch. Int. Med.*, 51: 122, 1933.
83. SOSKIN, S., KATZ, L. N. and FRISCH, R. The dual nature of the action of insulin upon the heart. *Ann. Int. Med.*, 8: 900, 1935.
84. MESSINGER, E. Cardiovascular changes associated with insulin shock treatment. *Ann. Int. Med.*, 12: 853, 1938.
85. GOODRICH, E. B. and JANNEY, F. Insulin hypoglycemia and the electrocardiogram. *J. Nerv. & Ment. Dis.*, 94: 10, 1941.
86. ERNSTENE, A. C. and ALTSCHULE, M. D. The effect of insulin hypoglycemia on the circulation. *J. Clin. Investigation*, 10: 521, 1931.
87. CRUICKSHANK, E. W. H. and SHRIVASTA, O. L. The action of insulin on the storage and utilization of sugar by the isolated normal and diabetic heart. *Am. J. Physiol.*, 92: 144, 1930.
88. CRUICKSHANK, E. W. H. Cardiac metabolism. *Physiol. Rev.*, 16: 597, 1936.
89. CANNON, W. B., McIVER, M. A. and BLISS, S. W. Studies on the conditions of activity in endocrine glands. XIII. A sympathetic and adrenal mech-

- anism for mobilizing sugar in hypoglycemia. *Am. J. Physiol.*, 69: 46, 1924.
90. STROUSE, S., SOSKIN, S., KATZ, L. N. and RUBINFELD, S. H. Treatment of older diabetic patients with cardiovascular disease. *J. A. M. A.*, 98: 1703, 1932.
 91. GREENE, R. Cardiac neurosis as a manifestation of hypoglycemia. *Lancet*, 2: 307, 1944.
 92. GOODSON, W. H. and WILLUS, F. A. Coronary thrombosis among persons less than forty years of age. *Minnesota Med.*, 22: 291, 1939.
 93. MIDDLETON, W. S. and OATWAY, W. H., JR. Insulin shock and the myocardium. *Am. J. M. Sc.*, 181: 39, 1931.
 94. NICELY, W. E. and EDMONDSON, C. C. The use of insulin in treatment of diabetes. Report of some cases. *Am. J. M. Sc.*, 167: 570, 1924.
 95. SMITH, K. S. Cardiac syndromes complicating diabetes and their treatment. *Brit. Heart J.*, 5: 1, 1943.
 96. GRALNICK, A. Pulmonary edema and electrocardiographic findings resembling coronary occlusion in insulin treatment. *Psychiatric Quart.*, 18: 650, 1944.
 97. WITTGENSTEIN, A. and MENDEL, B. Electrocardiogram after insulin. *Klin. Wchnschr.*, 3: 1119, 1924.
 98. LAUTER, S. and BAUMANN, H. Kreislauf und Atmung im hypoglykämischen Zustand. *Deutsche Arch. f. klin. Med.*, 163: 161, 1929.
 99. CITRON, J. Experiments on insulin. *Med. Klinik.*, 20: 1362, 1924.
 100. VON HAYNAL, E. Action of insulin on the heart. *Klin. Wchnschr.*, 4: 403, 1925.
 101. FREY, E. Antagonism of insulin and atropine. *Klin. Wchnschr.*, 4: 501, 1925.
 102. KUGELMAN, B. Zur Frage der Adrenalinausschüttung bei der Insulinhypoglykämie und bei Polschen Gefässkrisen. *Klin. Wchnschr.*, 12: 1488, 1933.
 103. HADORN, W. Untersuchungen über die Beeinflussung des Herzens durch Insulin und Hypoglykämie. *Ztschr. f. klin. Med.*, 130: 643, 1936.
 104. HADORN, W. and WALTHARD, B. Experimentelle Untersuchungen über anatomische Herzmuskelveränderungen im Insulinschock. *Ztschr. f. d. ges. exper. Med.*, 105: 174, 1939.

Seminars on Antibiotics

Chloramphenicol (Chloromycetin) in the Treatment of Infectious Diseases*

JOSEPH E. SMADEL, M.D.

Washington, D. C.

CHLORAMPHENICOL is one of the important recent additions to the group of antibiotics of proved clinical value. It is effective against a wide variety of infectious agents in the laboratory and on the ward. The purified crystalline form of the antibiotic, obtained from the fermentation products of the mold *Streptomyces venezuelae*, was used in most of the early laboratory and clinical studies. The active material was shown to have a relatively simple chemical structure and shortly thereafter it was produced synthetically on a practical basis and made available for clinical use.

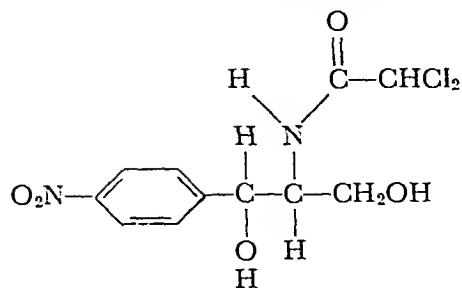
HISTORY OF DEVELOPMENT AND SYNTHESIS

During the course of a systematic search for new antibiotic agents a *Streptomyces* species which possessed antibiotic properties against several bacterial organisms was isolated by Dr. Paul R. Burkholder of the Osborn Botanical Laboratory at Yale University from a sample of soil collected in Venezuela. This culture, together with a number of others which showed promise, was given to the Research Laboratories of Parke, Davis and Company. The results of a series of integrated investigations by workers in the Research Laboratories^{1,2,3} indicated that (1) a substance with marked antibiotic activities was readily obtained from filtrates of Burkholder's organism (which was subsequently named *Strepto-*

myces venezuelae) when grown in large tanks, (2) the antibiotic activity of the filtrates was attributable to a stable substance obtained in crystalline form and named Chloromycetin, (3) the crystalline antibiotic was well absorbed when administered orally to laboratory animals and (4) the new material was of low toxicity for animals. While the early work on the spectrum of organisms affected by the new antibiotic was devoted primarily to a study of bacterial species, exploratory studies with *Rickettsia prowazeki* suggested that this rickettsial agent might also be susceptible.¹ At this point a third group of investigators, those at the Army Medical Department Research and Graduate School, began a series of studies designed to determine the efficacy of the antibiotic against viral and rickettsial agents.^{4,5,6} These focused attention on the marked antirickettsial properties of the antibiotic and on the low toxicity of Chloromycetin for man.⁷ The results of laboratory studies stimulated clinical trials in which patients with rickettsial diseases were treated with the newly recognized substance.

Crystalline Chloromycetin obtained by the fermentation process provided the biochemists in the Research Laboratories at Parke, Davis and Company with suitable material for studies on the chemical structure of the antibiotic. Chloromycetin proved to be a rather simple substance; according to Rebstock, Crooks, Controulis and Bartz⁸ its structural formula is:

* From the Department of Virus and Rickettsial Diseases, Army Medical Department Research and Graduate School, Army Medical Center, Washington, D.C.



The authors state, "Chloramphenicol is, so far as we know, the first naturally occurring compound which contains a nitro group or which is a derivative of dichloroacetic acid." These workers proved the validity of their formula by synthesizing the material and demonstrating that this substance had all of the physical and chemical properties of the natural antibiotic obtained by the fermentation process.⁹ The synthesized drug was promptly shown to be as efficacious in the treatment of experimental animals and of patients as was the natural substance obtained from the mold.¹⁰

The generic name chloramphenicol was given to the new antibiotic and the term Chloromycetin designated as a trade mark.

EFFECT OF CHLORAMPHENICOL ON MICROBIAL AGENTS

Rickettsiae and Viruses. Chloramphenicol was originally recognized and developed because of its *in vitro* antibacterial effects. However, its antirickettsial properties rapidly assumed paramount importance. It will be recalled that in 1947 no highly satisfactory chemotherapeutic agent existed for the treatment of the rickettsial diseases of man.¹¹

Viruses and rickettsiae are obligate intracellular parasites which multiply only in the presence of living cells. Past experience has shown little correlation between the capacity of various substances to inactivate these microbial agents *in vitro* with their capacity to inhibit growth of the agents *in vivo*. Therefore, in our screening program no attempt is made to determine *in vitro* destruction of viruses or rickettsiae until after a given substance has shown promise *in vivo*. Thus initial studies with new substances are performed as chemoprophylactic or chemo-

therapeutic tests using infected rodents or embryonated eggs.

Table I summarizes the available information on the inhibitory effect of chloramphenicol on the growth of a number of rickettsiae and viruses. Since the tabular data are derived from *in vivo* experiments which vary somewhat in design from one infectious agent to another, it is not feasible to express the degree of inhibition numerically. It is apparent from the table that all of the rickettsial agents which have been tested with chloramphenicol are markedly inhibited *in vivo*. Members of the psittacosis-lymphogranuloma venereum group of viruses, which are so closely related to the rickettsiae that they are classified as members of the family Chlamydozoaceae of the order Rickettsiales Gieszczykiewicz in the sixth edition of Bergey's "Manual of Determinative Bacteriology," are also markedly inhibited by this antibiotic. In sharp contrast, none of the other viruses is affected.

Certain of the experimental rickettsial infections appear to respond more readily to chloramphenicol than others. For example, when tested in embryonated eggs a significant prolongation of life of the embryos is obtained when 0.0625 mg. of drug is injected on one occasion into eggs infected with the agent of spotted fever, whereas 0.5 mg. is required to obtain a significant effect in embryos infected with the agent of Q fever.⁶ In such experiments as these the prolongation of life of embryos is equally great whether the drug is administered immediately before inoculation of infectious material or a day or so later. Even within a given species of rickettsiae certain strains may be more susceptible to chemotherapy than others. This is illustrated by the response of groups of mice infected with the Karp and the Seerangayee strains of *R. tsutsugamushi*. Daily administration of 2.5 mg. of chloramphenicol per mouse for twelve days after inoculation results in survival of all animals infected with the Karp organism and in death of practically all animals infected with the Seerangayee strain. Prolongation of treatment for twenty

days permits survival of practically all mice infected with Seerangayee. It should be mentioned that in such experiments as these, death occurs in infected untreated animals during the third week after inoculation.⁶

Chloramphenicol has no direct rickettsiocidal effect when tested *in vitro* in con-

TABLE I

INHIBITORY EFFECT OF CHLORAMPHENICOL ON GROWTH OF RICKETTSIAE AND VIRUSES IN LABORATORY

Agent and Reference	Inhibition
Rickettsiae:	
Epidemic typhus ^{1,4}	Marked
Murine typhus ⁴	Marked
Scrub typhus ⁴	Marked
Rocky Mountain spotted fever ⁴	Marked
Rickettsialpox ⁴	Marked
Q fever ⁶	Marked
Viruses:	
Lymphogranuloma venereum ^{4,5}	Marked
Psittacosis ^{4,5}	Marked
Variola-vaccinia ^{4,12}	None
Influenza A, A' and B ^{4,12}	None
Mumps ¹²	None
Lymphocytic choriomeningitis ¹⁴	None
Eastern equine encephalomyelitis ¹⁴	None
Western equine encephalomyelitis ¹⁴	None
St. Louis encephalitis ³	None
Japanese encephalitis ⁴	None
Rabies ³	None
Poliomyelitis (Lansing, Yalc-SK) ¹³	None
Mouse encephalomyelitis ¹³	None
Distemper ¹²	None
Newcastle disease ³	None
Chick bronchitis ¹²	None
Laryngotracheitis ¹²	None

centrations of 1250 $\mu\text{g}/\text{ml}$. against either *R. tsutsugamushi* or the virus of psittacosis. Furthermore, in at least several of the experimental infections which are benefited by chloramphenicol the therapy does not result in sterilization of tissues. This has been carefully studied in mice infected with *R. tsutsugamushi*. Here viable organisms may be recovered from the spleens of infected mice 100 days after inoculation despite the fact that the animals have received a full therapeutic dose of 2.5 mg. per day during the entire period of time.⁶ With certain of the other agents, i.e., *R. rickettsii* and *R. akari*, preliminary data suggest that actual sterilization of the tissues may occur in some of the animals which recover from infection. However, it may be that auto-sterilization occurs rather promptly in

experimental animals which survive infection with these particular agents. The subject of mode of action of chloramphenicol will be discussed in a general way in other sections of this review. Suffice it to say here that in scrub typhus infections in man and

TABLE II

IN VITRO SENSITIVITY OF BACTERIA TO CHLORAMPHENICOL *

Organism	Inhibiting Concentration $\mu\text{g}/\text{ml}$. †
<i>Alcaligenes fecalis</i>	1.0
<i>Bacillus anthracis</i>	1.0-5.0
<i>Brucella abortus</i>	2.5-10
<i>Clostridia</i> (genus).....	>500
<i>Corynebacterium diphtheriae</i>	0.5
<i>Diplococcus pneumoniae</i>	1.0-2.5
<i>Escherichiae coli</i>	2.5
<i>Hemophilus influenzae</i>	3.6 ‡
<i>Hemophilus pertussis</i>	0.2
<i>Klebsiella pneumoniae</i>	0.5-2.5
<i>Malleomyces mallei</i>	40
<i>Mycobacterium tuberculosis</i>	6-12
<i>Neisseria meningitidis</i>	2.5
<i>Pasteurella</i> (genus).....	0.2-2.5
<i>Proteus</i> (genus).....	1-25
<i>Pseudomonas</i> (genus).....	10-100
<i>Salmonella enteritidis</i>	0.7-2.5
<i>Salmonella paratyphi</i>	0.7
<i>Salmonella schottmuelleri</i>	0.5-2.5
<i>Salmonella typhosa</i>	1-5.0
<i>Shigella dysenteriae</i>	0.7
<i>Shigella paradysenteriae</i>	0.5-2.5
<i>Shigella sonnei</i>	2.5-5.0
<i>Streptococcus pyogenes</i> (hemolyticus).....	0.7-2.5
<i>Vibrio comma</i>	1.0

* Information from McLean et al.¹²

† Minimum inhibiting concentrations were determined on the basis of complete inhibition of growth of the designated organism in fluid medium at eighteen hours.

‡ From Dr. T. E. Woodward, personal communication.

mouse chloramphenicol does not "cure" the patient; the antibiotic suppresses growth of the rickettsiae and permits the individual to develop his immune processes and thus to recover from the disease.

Bacteria. Chloramphenicol has an inhibitory effect on the growth *in vitro* of a wide range of bacteria. A number of the early publications contained lists of organisms with their susceptibility to chloramphenicol as determined by one of several methods.^{1,3,15,16} The recent report by Mc-

Lean and his associates¹² presents the most extensive single list currently available, moreover all organisms mentioned were tested by a single method. Information contained in Table II has been taken almost entirely from this source.¹² The tabular data indicate the minimum concentration of chloramphenicol required to cause complete inhibition of growth in fluid medium of a number of bacterial species which are pathogenic for man.

Inspection of Table II reveals a preponderance of gram-negative bacteria. Chloramphenicol does indeed possess considerable activity against gram-negative organisms. While inhibition of growth of staphylococci and streptococci is obtained, the concentrations required to affect these organisms are far in excess of the effective concentrations of penicillin. Such information as that given in Table II is of interest to the physician early in the work with a new antibiotic since it supplies leads which may be of value in experimental chemotherapy studies in animals and in man. In fact, demonstrable effectiveness *in vitro* of a new antibiotic against a number of bacteria of medical importance is usually a prerequisite for continued general interest in that substance. However, unless such an antibiotic possesses many other satisfactory characteristics, the new substance remains a matter of academic interest to a few laboratory workers.

It would be pertinent in a review of this type to present extensive experimental evidence of the chemotherapeutic effect of chloramphenicol against a number of experimental bacterial infections in animals. While a certain amount of such information is available, it is extremely limited. This is due in part to the fact that early in its history chloramphenicol was used in the treatment of patients with rickettsial disease, and subsequently was employed in bacterial infections of man without waiting for the results of the usual laboratory experimentation. This is illustrated in the successful treatment with chloramphenicol of patients suffering from typhoid fever.¹⁷ An even

more extreme example is found in its use in the satisfactory treatment of acute gonorrheal urethritis in the male;¹⁸ here laboratory data are still not available on the *in vitro* effect of chloramphenicol on *Neisseria gonococcus*.

The work of Youmans and his colleagues on the tuberculostatic action of chloramphenicol in mice is encouraging and deserves to be extended, particularly since the blood levels obtained in the treated mice were well below those which can be produced readily in human beings.¹⁹ Gauld and his co-workers²⁰ demonstrated the efficacy of chloramphenicol in mice inoculated with *Vibrio comma*. However, they pointed out the difficulties which would accompany chemotherapy of cholera in man and suggested that its principal use in this infection might be as a prophylactic agent during an epidemic.

Woodward and his co-workers²¹ found that chloramphenicol had little beneficial effect in mice treated for three days after infection with *Pasteurella tularensis*. Under these same conditions streptomycin gave somewhat more satisfactory results but aureomycin was superior to the other two antibiotics. Smith and his colleagues make the following statement:³ "Exploratory experiments, using small numbers of mice infected intraperitoneally with lethal doses of virulent *Klebsiella pneumoniae* (type A), *Shigella paradysenteriae* (Flexner), *Shigella paradysenteriae* (Sonne), *Diplococcus pneumoniae* (type 1), *Streptococcus hemolyticus*, and *Streptococcus viridans* and treated subcutaneously with chloromycetin in 20 per cent propylene glycol, streptomycin sulfate, or penicillin G, showed that chloromycetin was qualitatively similar to streptomycin but quantitatively inferior in protective action."

The results obtained when mice were infected with *Salmonella typhimurium* and treated with chloramphenicol were considered by Seligmann and Wassermann²² to be discouraging. It is to be noted that their treated mice survived during the relatively short period of therapy but subsequently died. This brings up several points which

are worth mentioning at this time. In the first place, chloramphenicol may be highly bacteriostatic for a given organism but almost completely lacking in bactericidal power for the same organism. Thus concentrations of 1000 $\mu\text{g}/\text{ml}$. in fluid media do not kill *S. typhosa*.^{17b} This is similar to the observation described earlier in which chloramphenicol had no *in vitro* rickettsiocidal activity against *R. tsutsugamushi*. With these two agents, at least, recovery of the individual must depend upon the development of immunity in the infected host since the antibiotic merely suppresses growth of the organisms. The situation in mice infected with *S. typhimurium* may be similar to that in man infected with *S. typhosa*. In the latter instance, if relapses are to be avoided, chloramphenicol therapy must be continued for longer than eight days.²³

Fungi. The majority of the fungi which have been examined are not affected by chloramphenicol. McLean and his associates¹² tested twenty-one strains from eleven genera of pathogenic fungi and sixteen strains from nine genera of non-pathogenic fungi. Growth of two representatives from the first group, namely, *Actinomyces bovis* and *Nocardia asteroides*, both of which are causal agents of actinomycosis, were completely inhibited by concentrations of 5 to 20 $\mu\text{g}/\text{ml}$. The remaining organisms in both groups were not inhibited appreciably by concentrations of 1000 to 2500 $\mu\text{g}/\text{ml}$.

Spirochetes. Experimental infection in rabbits caused by Nichols strain of *Treponema pallidum* was not affected by daily doses of 25 mg. of chloramphenicol per Kg. of body weight. Double and quadruple this amount cleared the lesions of spirochetes and permitted healing temporarily.³ These preliminary results suggest that chloramphenicol does not compare favorably with penicillin in the therapy of experimental syphilis.

Spirochetes of relapsing fever, *Borrelia novyi* and *B. recurrentis*, were immobilized by chloramphenicol *in vitro* and infection in mice with the first organism was suppressed appreciably by small doses of the drug.^{3,12}

Protozoa. Chloramphenicol had no appreciable antimalarial effect when tested in ducks and chickens infected with *Plasmodium lophurae*.³ High concentrations of the drug did not affect *Trichomonas foetus* but in certain culture media reduced the number of *Endamoeba histolytica*. The latter observation in itself may be of little importance since the result may have been an indirect one involving the bacteria which occur in the cultures and serve as a nutrient supply for the ameba. Of greater significance, however, is the observation that an appreciable clearing of infection occurred in rats and dogs with experimental amebiasis which were given large doses of drug.¹²

Development of Resistance by Micro-organisms. McLean and his co-workers¹² have shown that resistant variants can be developed from a number of species of bacteria which were originally susceptible to chloramphenicol. This was done in the usual manner, i.e., growing the culture in increasing concentrations of the antibiotic.

Neither the experience of these workers nor that in our laboratory⁶ has presented evidence that drug-resistant strains of rickettsiae can be developed under experimental conditions.

It is noteworthy that clinical experience in the treatment of typhoid fever and scrub typhus has provided no indication that resistant strains make their appearance in treated patients.^{17,24} Thus it would appear that this phenomenon may be expected to be of little importance to the physician.

LABORATORY METHODS FOR DETERMINATION OF CHLORAMPHENICOL LEVELS

Chloramphenicol is an extremely stable compound. It is unaffected over the pH range from 2-9 or by boiling in distilled water for a number of hours.² The solubility of the neutral, white crystalline drug in distilled water is 0.25 per cent. Solutions of this concentration may be kept for months at icebox temperatures for use as the standard in assays for chloramphenicol. Solutions containing less than 1.0 mg. per ml. deteri-

orate after a few days or weeks of storage in the refrigerator.

Bioassay. A number of the methods which have proved suitable for assaying other antibiotics have been used with chloramphenicol.^{1,3,12,15,16,19} At the Army

Bratton and Marshall for determination of sulfonamide. As would be expected under these circumstances the presence of sulfonamides interferes with the test.

About 10 per cent of the chloramphenicol administered to human beings and dogs is

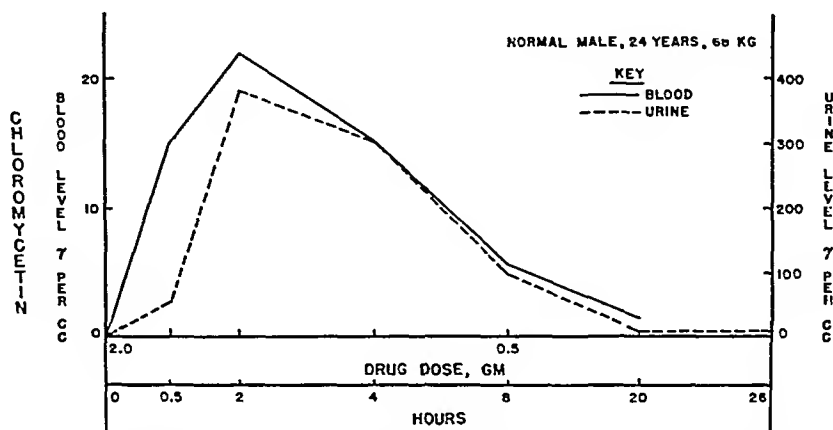


FIG. 1. Blood and urine levels of chloramphenicol following a 2.0 Gm. oral dose. Determinations were by the bioassay method. (Reproduced from *Proc. Soc. Exper. Biol. & Med.*, 68: 9-12, 1948.⁷)

Medical Department Research and Graduate School a modification of the turbidimetric method of Ehrlich and his associates³ has been used most extensively. In this technique the amount of crystalline drug in a known standard solution which is required to produce 50 per cent inhibition of growth of *Shigella sonnei* is compared spectrophotometrically with the inhibiting capacity of varying dilutions of the unknown material. The method determines the amount of biologically active chloramphenicol and is satisfactory for estimating the drug levels in serum, urine and spinal fluid and, with some slight modifications, milk and bile.

Chemical Method. The chemical method for determining chloramphenicol, as described by Glazko and his associates,²⁵ is based on the reduction of the nitro group of the chloramphenicol molecule to a primary amine (this is effected by heating with zinc dust) followed by diazotization and coupling. The color produced by this reaction is proportional to the concentration of chloramphenicol. In essence, after conversion to the primary amine the method is essentially identical with the procedure of

excreted in the urine in the active form and is detectable by bioassay. In dogs most of the administered chloramphenicol appears in the urine in the form of inactive nitro compounds which, like the active substance, react in the chemical determination for chloramphenicol. In human beings most of the chloramphenicol is excreted in an inactive conjugated form, probably as the monoglucuronide.²⁵

Since relatively small amounts of the degradation forms of the drug are present in blood and spinal fluid, the chemical determination gives a close approximation of the amount of biologically active antibiotic which is present. On the other hand, the occurrence of large amounts of degradation products in the urine interferes with the chemical estimation of the amount of active drug.

Levels of Chloramphenicol in Body Fluids of Man. Figure 1 illustrates the levels of chloramphenicol attained in the blood and urine of a normal person following the oral administration of a single 2.0 Gm. dose of drug. These data, obtained by bioassay, indicate that the drug is rapidly absorbed

from the gastrointestinal tract and reaches appreciable levels in both blood and urine within one-half hour.⁷ The maximal blood levels, which are usually of the order of 20 to 40 $\mu\text{g}/\text{ml}$. following a 2.0 Gm. dose and 40 to 60 $\mu\text{g}/\text{ml}$. after a 4.0 Gm. dose, are reached within one to three hours. The values gradually decline and no detectable antibiotic is found at eighteen to twenty-four hours. The levels of active material in the urine are appreciably higher than in the blood but the rise and fall follow the same general pattern. The amounts of chloramphenicol in the spinal fluid, bile and milk of human beings are about half those found simultaneously in the blood.^{17b, 24b}

CLINICAL USE OF CHLORAMPHENICOL

Rickettsial Diseases

Typhus Fevers (Epidemic, Murine and Scrub). The early laboratory studies indicated that chloramphenicol might be of value in the treatment of rickettsial diseases. Since satisfactory therapeutic measures were particularly needed for this group of infections, the first clinical trials of the new drug were made with patients suffering from typhus fever during the winter of 1947 and 1948 in Bolivia²⁶ and in Mexico.²⁷ These initial observations provided highly encouraging results but both tests left something to be desired. Although carefully studied the Mexican patients with epidemic and murine typhus were few in number. On the other hand, while a larger group of patients was treated in Bolivia during an epidemic of louse-borne typhus, facilities were not available for the extensive study of individuals. Additional results with chloramphenicol in the treatment of patients with epidemic and murine typhus have not been reported, nevertheless, these two preliminary trials have received much indirect support from the results of therapeutic studies with this antibiotic in patients with two other rickettsial diseases, i. e., scrub typhus and Rocky Mountain spotted fever. There is little point in discussing the therapeutic regimens employed in the first groups of typhus fever

patients who were treated with chloramphenicol since subsequent studies have provided information which should now be applied to these two diseases.

The work in Malaya of the U. S. Army Scrub Typhus Research Team on the treat-

TABLE III
SCRUB TYPHUS PATIENTS
KUALA LUMPUR, 1948*

	Treated	Untreated
No. patients.....	30 23 males 7 females	19 16 males 3 females
Day after onset R _x begun.....	3 to 11, av. 6.2	
Last febrile day of illness.....	4 to 12, av. 7.4	12 to 31 av. 17.1
Duration of fever after R _x begun (hr.).....	6 to 96, av. 31.8	
Day after onset dis- charged from hos- pital.....	14 to 28, av. 17.8	17 to 51 av. 29.9
Complications....	0	1 parotitis 1 pneumonia
Deaths.....	0	1 17th day
Month of onset....	March-Sept.	Feb.-June

* Reproduced from Smadel, Woodward, Ley and Lewthwaite.^{24b}

ment of tsutsugamushi disease provided conclusive evidence of the efficacy of chloramphenicol in the therapy of rickettsial diseases.²⁴ The data on the first thirty patients with naturally acquired scrub typhus who received this new antibiotic are summarized in Table III.

The typical response of a treated patient in this series is illustrated graphically in Figure 2. All of the Malayan patients received an initial oral dose of 3.0 to 4.0 Gm. of chloramphenicol. This was followed by 0.25 Gm. amounts at intervals of two to three hours for a varying period of time. The first patients were treated over a period of five or six days but subsequent observations showed that such long periods of therapy were unnecessary. Indeed, a single oral dose of 3.0 to 4.0 Gm. of drug was sufficient to control the disease in a number of patients who received this regimen. However, the ultimate practice

was to give an initial loading dose of 3.0 or 4.0 Gm. and follow this with 0.25 Gm. every three hours during the succeeding twenty-four hours.

Chloramphenicol has been used prophylactically in human beings exposed to scrub

phenicol is rickettsiostatic but not rickettsiocidal. It would appear that suppression must be maintained long enough for the individual to develop immunity if he is to remain asymptomatic when the drug is discontinued.

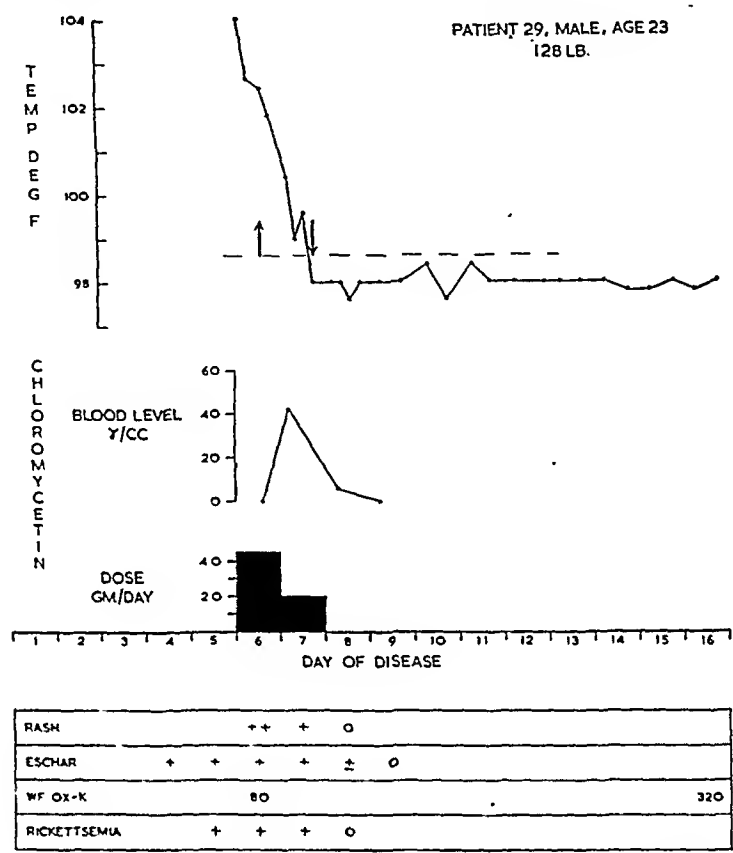


FIG. 2. Clinical response of patient with scrub typhus to chloramphenicol therapy begun on the sixth day of disease. A total of 6.5 Gm. of chloramphenicol was given over a period of twenty-two hours. (Reproduced from *J. Clin. Investigation*, 28: 1196, 1949.²⁴)

typhus. It has been shown that daily oral doses of 1.0 Gm. or weekly doses of 4.0 Gm. are sufficient to suppress clinical evidence of disease in volunteers who were exposed in hyperendemic areas of scrub typhus in Malaya. When prophylaxis was continued for only two weeks after the end of exposure, scrub typhus developed in the volunteers about a week after the last prophylactic dose of drug.²⁸ However, when the regimen was continued for four weeks after the last exposure, none of the volunteers subsequently developed clinical disease.²⁹ Here again the evidence indicates that chloram-

Spotted Fever. Pincoffs and his co-workers³⁰ obtained excellent results with chloramphenicol in the treatment of fifteen patients suffering from Rocky Mountain spotted fever. These persons, who were carefully studied during the spring and summer of 1948, were given an initial oral loading dose of 75 mg. per Kg. of body weight followed by 0.5 Gm. every three hours until the temperature had been normal for a twenty-four-hour period. The average duration of fever after initiation of therapy was approximately 2.2 days. The duration of the febrile response in each of

the fifteen cases is presented graphically in Figure 3. A number of the patients were desperately ill but all recovered.

For comparison the Baltimore group analyzed the records of forty-six patients with spotted fever who were treated at the University Hospital between 1930 and 1946 and who recovered without benefit of specific therapy and without complications. The average duration of fever in these cases was 16.0 days. The authors point out that in Maryland during the past decade the mortality from Rocky Mountain spotted fever has been about 20 per cent.

General Remarks. In general, a therapeutic schedule which seems applicable to adult patients suffering from the rickettsial diseases is as follows: An initial loading dose of 3.0 to 4.0 Gm. of chloramphenicol given by mouth, followed by 0.25 Gm. doses every two or three hours until the temperature returns to a normal level. Such a schedule usually requires 5.0 to 10.0 Gm. of drug over a period of one to three days.

Reports have not yet appeared on the use of chloramphenicol in patients with Q fever or rickettsialpox, both of which diseases occur in the United States. Laboratory data on experimental infections caused by the agents of these rickettsial diseases would lead to the belief that the drug should be useful in the treatment of such patients.

Bacterial Diseases

Typhoid Fever. Two patients originally presumed to have scrub typhus and treated with chloramphenicol by the American group in Malaya subsequently were proved to have typhoid fever; these patients became afebrile in three to four days. As a result studies on this disease were pursued intensively. The data obtained from the first ten cases of typhoid fever who received chloramphenicol clearly indicated that the antibiotic had a specific therapeutic effect in this bacterial disease. The average duration of fever in this group of patients after treatment was instituted was 3.5 days.^{17a} The graphic record of one of the first patients is presented in Figure 4.

The extensive experience of the Army group, gained in the treatment of forty-four patients with typhoid fever, confirmed the early observations.^{17,23} These investigators pointed out that the patients became afebrile before the intestinal lesions of

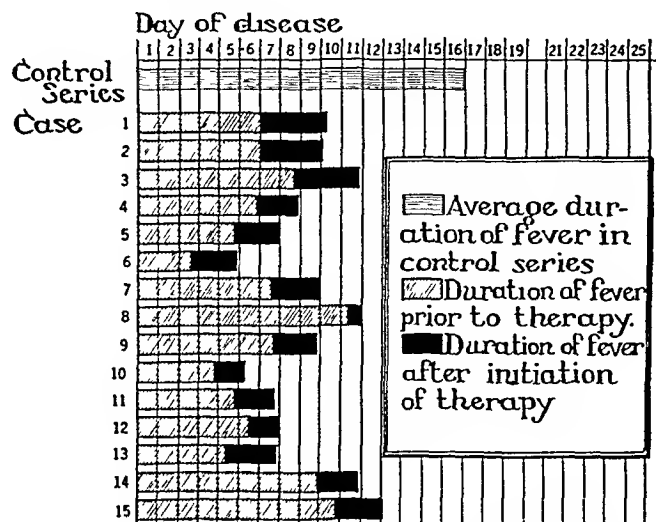


FIG. 3. Duration of fever in fifteen cases of Rocky Mountain spotted fever treated with chloramphenicol contrasted with average duration of fever in control series of forty-six cases. (Reproduced from *Ann. Int. Med.*, 29: 656-663, 1948.³⁰)

typhoid fever healed and as a result hemorrhage and perforation sometimes occurred during or shortly after defervescence. In their summary of the first twenty-four patients treated they reported intestinal hemorrhage in two persons and intestinal perforation in another. Nevertheless, all of these treated patients recovered.^{17b}

The Army group encountered relapses of typhoid fever in two of the first ten treated patients. Subsequent studies demonstrated that the incidence of relapses was related to the duration of chloramphenicol therapy.²³ Thus a clinical relapse with reappearance of bacteremia occurred in seven of the thirteen patients whose initial course of drug was given for eight days or less; the average duration of therapy was 6.9 days. No relapses occurred in another group of nineteen patients which was comparable in essentially all respects except that the treatment was continued for nine to fourteen days, average 11.2. Similarly, no relapses were encountered in a third group of twelve patients whose therapy was continued for

fourteen to twenty-three days. On the basis of these findings it would appear that patients with typhoid fever should receive 25 to 30 Gm. of chloramphenicol over a period of ten to twelve days. This can be given in the following manner: After an oral

appear to be higher in the treated group than it was in the large groups of patients who recovered before the advent of specific therapy.^{17b} Chloramphenicol appears to be of no value in eradicating the carrier state of typhoid fever.^{17b,31}

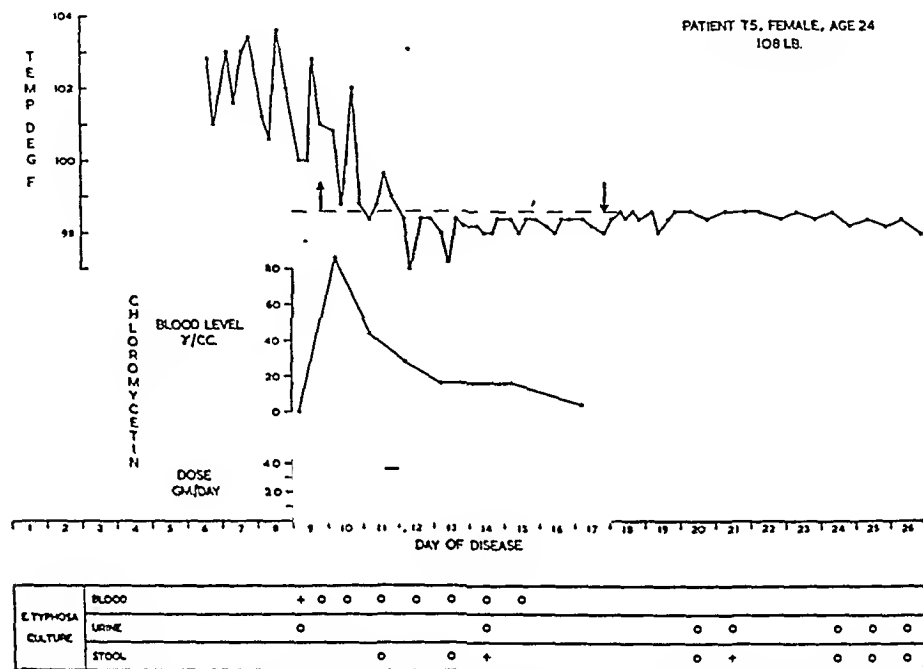


Fig. 4. Clinical response of typhoid patient to chloramphenicol therapy. A total of 22 Gm. was given over a period of nine days. (Reproduced from *Ann. Int. Med.*, 29: 131-134, 1948.^{17a})

loading dose of 3.0 Gm. the patient may be given a total of 3.0 Gm. daily in divided doses until the fever disappears. Subsequently the patient should receive 2.0 Gm. daily for the next eight to ten days.

In general, *S. typhosa* were no longer demonstrable in the bloods of the patients a few hours after chloramphenicol therapy was begun. Furthermore, the blood remained sterile thereafter except in those instances in which relapses occurred. About one-half of the patients had *S. typhosa* in their stools on one or more occasions after chloramphenicol therapy was begun. Stools from the majority of these did not yield the organisms after therapy was discontinued; indeed, the reappearance of *S. typhosa* in the stool was limited almost entirely to those individuals who suffered relapses. The incidence of the typhoid carrier state did not

Confirmatory evidence regarding the value of chloramphenicol in the treatment of typhoid fever has accumulated rapidly. McDermott and his associates during the course of therapeutic trials in Mexico in the fall of 1948 reported experiences similar to those of the Army group in Malaya.³² More recently the drug has been shown to be of value in the treatment of a number of patients with this disease in the United Kingdom^{33,34} and the United States.³⁵

Brucellosis. Woodward and his associates³⁶ reported on the results of administering chloramphenicol to nine patients with brucellosis. Six of these were experiencing an initial attack and three were suffering a relapse which had begun two to five months after the primary illness had been controlled by combined streptomycin and sulfadiazine therapy. In four of the patients *Brucella*

abortus was cultured from the blood, in two *B. suis* and in one *B. melitensis*. The diagnosis in the two remaining cases was established by agglutination tests. The clinical record of one of these patients is reproduced graphically in Figure 5. The

phenicol and aureomycin, was the drug of choice for this disease.

Harris' experience, although more extensive than that of Woodward, provided less definitive information. Among the 110 patients with brucellosis who were treated

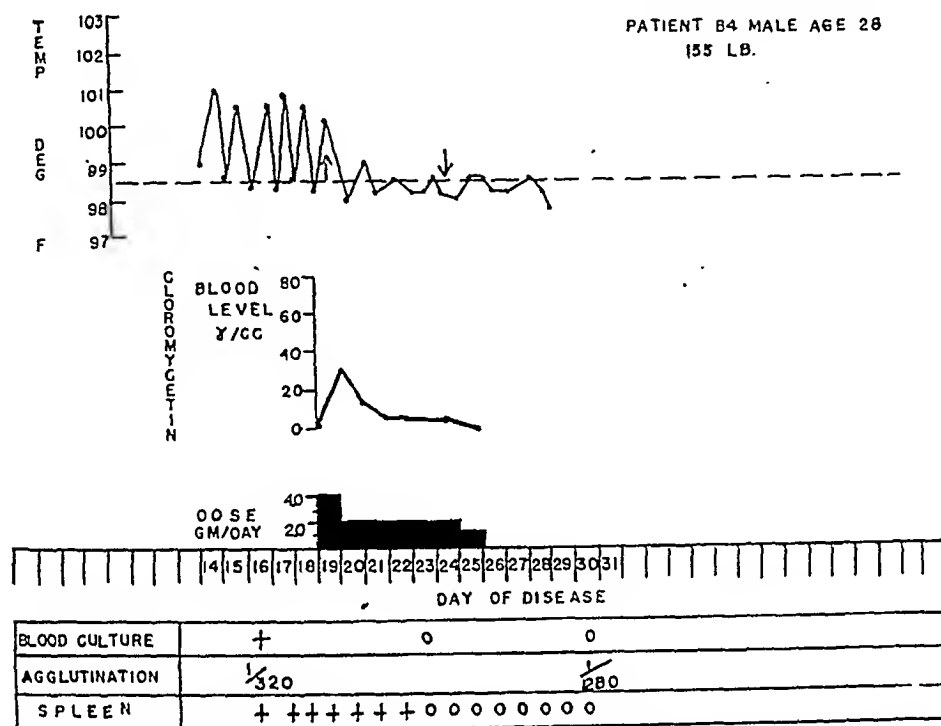


FIG. 5. Clinical response of patient with brucellosis (*B. suis*) treated with 15.5 Gm. of chloramphenicol over a period of seven days. (Reproduced from *J. Clin. Investigation*, 28: 968, 1949.³⁶)

average duration of fever after therapy was begun was 2.7 days for the nine patients.

The therapeutic regimen employed in this group of patients was similar to that used in typhoid fever. Following the initial loading dose of approximately 50 mg. of chloramphenicol per Kg. of body weight, the patients were given 0.25 Gm. doses at three-hour intervals until the temperature became normal and for a minimum of five days thereafter. The majority of patients were followed for six to nine months after treatment. One individual suffered a relapse thirty days after chloramphenicol was discontinued. This febrile episode was promptly terminated when therapy was again instituted.

The authors concluded that chloramphenicol was superior to the earlier forms of treatment. They also concluded that at this time it was impossible to decide which of the two new antibiotics, i. e., chloram-

with aureomycin and twenty-five who received chloramphenicol, the diagnosis was proved culturally in only one instance.³⁷

Gonorrhea. During the work of the Army research team in Malaya one of the volunteers in a scrub typhus chemoprophylactic test developed acute gonorrheal urethritis shortly before he was due to receive his first oral dose of 3.0 Gm. of chloramphenicol. Treatment of the urethritis was delayed in order to see what effect the scheduled dose of chloramphenicol would have on the gonorrheal infection. The discharge in this individual cleared within twenty-four hours after the drug was given. Subsequently a total of forty-eight Malayan males with acute gonorrheal urethritis were treated with a single oral dose of 1.0 to 1.5 or 3.0 to 3.5 Gm. of either fermentation or synthetic chloramphenicol.¹⁸ The clinical response was essentially the same in each subgroup. Dysuria disappeared within thirty-six hours

(average for the forty-eight patients) and discharge (as determined by the absence of exudate on stripping) within forty-nine hours. Smears of the discharge with few exceptions were free of gonococci by the next day and leukocytes generally were absent from the discharge in those instances in which this sign persisted longer than forty-eight hours. Ten patients, or approximately 20 per cent of this entire series, had relapses during the month following treatment. There was no apparent difference in the number of recurrences in the various subgroups. All patients with relapses were treated with a single oral 3.0 Gm. dose of chloramphenicol and all responded satisfactorily.

The authors were of the opinion that the therapeutic results in this infection compared favorably with those obtained by other methods of therapy. They pointed out that chloramphenicol appeared to have limited effect in experimental syphilis in rabbits and that their results in two patients with syphilitic chancres were essentially comparable to those reported in infected rabbits. Therefore, it seemed possible that doses of chloramphenicol which were adequate to cure the Neisserian infection might not suppress a syphilitic infection which was in the incubation period.

Other Bacterial Infections. There are a number of reasons why chloramphenicol should be of value in the treatment of urinary tract infections. In the first place, larger amounts of antibiotic are found in the urine than in the blood. Secondly, many of the bacteria commonly found in urinary tract infections are readily inhibited by the antibiotic. Chittenden and his co-workers³⁸ found that the urine of infected patients became free of bacteria within a day or so after chloramphenicol treatment was instituted in the form of 1.0 to 3.0 Gm. daily. These workers emphasized that complicating factors which interfere with urinary flow must be corrected if the infection is to be permanently controlled.

The causal organisms of a number of bacterial diseases of man are susceptible to

chloramphenicol. Although reports of the use of this new antibiotic in the treatment of patients with these diseases have not yet appeared in the literature, they will be awaited with interest. Some of these infections are whooping cough, influenzal meningitis, Friedländer's pneumonia, plague, bacillary dysentery, cholera, melioidosis and perhaps even tuberculosis.

CHLORAMPHENICOL IN OTHER INFECTIOUS DISEASES OF MAN

One published report has appeared on the use of chloramphenicol in a patient with atypical pneumonia associated with the development of cold agglutinins.³⁹ The results of future experience in the therapy of this disease must be awaited before any conclusions are warranted. It will be recalled that atypical pneumonia is a clinical syndrome having a variety of etiologic agents but that the causal agent of the disease associated with the cold agglutination phenomenon has not been transmitted to animals.⁴⁰ Chloramphenicol is effective against *R. burneti* and the virus of psittacosis, both of which may produce pulmonary disease indistinguishable from primary atypical pneumonia of unknown etiology. Therefore, in future studies it will be important to employ all of the available diagnostic procedures in order to establish the etiology of each case of treated atypical pneumonia.

The experimental infections with the virus of lymphogranuloma venereum, which is closely related to the agent of psittacosis, are readily controlled by chloramphenicol. It is to be expected that the drug will prove of value in treating human disease caused by this virus.

Another of the venereal diseases, i. e., granuloma inguinale, appears to respond to chloramphenicol. Greenblatt and his associates⁴¹ reported good results in five patients with this infection who received 20 Gm. of drug over a period of five to ten days. Donovan bodies were no longer demonstrable in the lesions a few days after therapy was begun.

Chloramphenicol has some *in vivo* effect on several members of the family Trepone-mataceae. Whether it will be of value in the treatment of patients with relapsing fever or with syphilis remains to be seen. The Army group in Malaya¹⁸ observed two patients with primary syphilis in whom the spirochetes disappeared and the primary lesion healed after several days of oral therapy. However, both of these individuals developed recurrent lesions at the sites of the original chancres about a month later. In view of the efficacy of established methods of antiluetic treatment, studies on chloramphenicol therapy in syphilis should be restricted to a few specialized centers until adequate evaluation is obtained.

TOXICITY OF CHLORAMPHENICOL FOR MAN

The presence of the nitrobenzene radical in the structure of chloramphenicol led to the suspicion that the drug might be toxic for the hemopoietic system. Careful observations on a relatively large number of patients with scrub typhus or with typhoid fever who were treated with the antibiotic have failed to show any significant change in the red blood cells or white blood cells attributable to therapy. Furthermore, none of these cases has shown evidence of renal or hepatic involvement.^{17,24}

Occasional individuals who receive large single doses have transient mild euphoria. A number of persons complain of mild gastrointestinal disturbances characterized by moderate gaseous distention and a slight change in the consistency of the feces for a few days. A few persons, limited almost entirely to the group receiving drug for a period of a week or more, develop glossitis. This is characterized by tenderness, hyperemia and marked prominence of lingual papillae. Glossitis continues during the period of therapy and for a few days after the drug has been stopped. After prolonged administration of the antibiotic pruritus ani has been noted in a few instances.⁴²

No serious toxic manifestations have occurred as a result of chloramphenicol therapy. In fact, the untoward reactions so

far observed have been minor in character. It must be realized, however, that the drug is only now coming into wide usage and careful search for such manifestations should be continued.

CONCLUSIONS

Chloramphenicol is a highly effective therapeutic agent against a number of infectious diseases of man. Among these the rickettsial diseases, typhoid fever, brucellosis and gonorrhea are presently in the foreground.

The drug has potential usefulness against other diseases caused by a wide variety of etiologic agents.

It is worth while to compare the experimental data summarized in this article with those dealing with aureomycin.⁴³ Both antibiotics are amazingly similar in their therapeutic effectiveness in a wide range of infections. Despite these similarities the two are not identical. The chemical structure of chloramphenicol is simple and the drug has been synthesized on a commercial scale; neither of these points applies to aureomycin. Chloramphenicol is a specific for typhoid fever while aureomycin is not. Neither drug appears to be dangerously toxic but annoying reactions are more frequent following aureomycin than chloramphenicol. The medical world is fortunate in having acquired within the past two years two such valuable antibiotics as chloramphenicol and aureomycin. It is safe to assume that the limits of application of both of these have not yet been reached.

REFERENCES

1. EHRLICH, J., BARTZ, Q. R., SMITH, R. M., JOSLYN, D. A. and BURKHOLDER, P. R. Chloromycetin: a new antibiotic from a soil actinomycete. *Science*, 106: 417, 1947.
2. BARTZ, Q. R. Isolation and characterization of Chloromycetin. *J. Biol. Chem.*, 172: 445-450, 1948.
3. SMITH, R. M., JOSLYN, D. A., GRUHZIT, O. M., MCLEAN, I. W., JR., PENNER, M. A. and EHRLICH, J. Chloromycetin: biological studies. *J. Bact.*, 55: 425-448, 1948.
4. SMADEL, J. E. and JACKSON, E. B. Chloromycetin, an antibiotic with chemotherapeutic activity in experimental rickettsial and viral infections. *Science*, 106: 418-419, 1947.
5. SMADEL, J. E. and JACKSON, E. B. Effect of Chloromycetin on experimental infection with psittacosis

- and lymphogranuloma venereum viruses. *Proc. Soc. Exper. Biol. & Med.*, 67: 478-483, 1948.
6. SMADEL, J. E., JACKSON, E. B. and CRUISE, A. B. Chloromycetin in experimental rickettsial infections. *J. Immunol.*, 62: 49-65, 1949.
 7. LEY, H. L., JR., SMADEL, J. E. and CROCKER, T. T. Administration of Chloromycetin to normal human subjects. *Proc. Soc. Exper. Biol. & Med.*, 68: 9-12, 1948.
 8. REBSTOCK, M. C., CROOKS, H. M., JR., CONTROULIS, J. and BARTZ, Q. R. Chloramphenicol (Chloromycetin). iv. Chemical studies. *J. Am. Chem. Soc.*, 71: 2458-2462, 1949.
 9. CONTROULIS, J., REBSTOCK, M. C. and CROOKS, H. M., JR. Chloramphenicol (Chloromycetin). v. Synthesis. *J. Am. Chem. Soc.*, 71: 2463-2468, 1949.
 10. SMADEL, J. E., JACKSON, E. B., LEY, H. L., JR. and LEWTHWAITE, R. Comparison of synthetic and fermentation chloramphenicol (Chloromycetin) in rickettsial and viral infections. *Proc. Soc. Exper. Biol. & Med.*, 70: 191-194, 1949.
 11. SNYDER, J. C. Treatment of rickettsial diseases. Chapter in *The Rickettsial Diseases of Man* Pp. 169-177. Washington, D. C., 1948. American Association for the Advancement of Science.
 12. McLEAN, I. W., SCHWAB, J. L., HILLEGAS, A. B. and SCHILINGMAN, A. S. Susceptibility of micro-organisms to chloramphenicol (Chloromycetin). *J. Clin. Investigation*, 28: 953, 1949.
 13. MELNICK, J. J. Quoted by McLEAN et al.¹¹
 14. SMADEL, J. E. and JACKSON, E. B. Unpublished data.
 15. GOTTLIEB, D., BHATTACHARYYA, P. K., ANDERSON, H. W. and CARTER, H. E. Some properties of an antibiotic obtained from a species of *Streptomyces*. *J. Bact.*, 55: 409-417, 1948.
 16. GREEN, R. and MANKIKAR, D. S. Afebrile cases of melioidosis. *Brit. M. J.*, 1: 308-315, 1949.
 17. a. WOODWARD, T. E., SMADEL, J. E., LEY, H. L., JR., GREEN, R. and MANKIKAR, D. S. Preliminary report on the beneficial effect of Chloromycetin in the treatment of typhoid fever. *Ann. Int. Med.*, 29: 131-134, 1948. b. WOODWARD, T. E., SMADEL, J. E. and LEY, H. L., JR. Chloramphenicol (Chloromycetin) in the treatment of typhoid fever. General observations. *J. Clin. Investigation*, (in press), 1949.
 18. SMADEL, J. E., BAILEY, C. A. and MANKIKAR, D. S. Preliminary report on the use of chloramphenicol (Chloromycetin) in the treatment of acute gonorrheal urethritis. *J. Clin. Investigation*, (in press), 1949.
 19. YOUNG, G. P., YOUNG, A. S. and OSBORNE, R. R. Tuberculostatic action of Chloromycetin *in vitro* and *in vivo*. *Proc. Soc. Exper. Biol. & Med.*, 67: 426-429, 1948.
 20. GAULD, R. L., SCHILINGMAN, A. S., JACKSON, E. B., MANNING, M. C., BATSON, H. C. and CAMPBELL, C. C. Chloramphenicol (Chloromycetin) in experimental cholera infections. *J. Bact.*, 57: 349-352, 1949.
 21. WOODWARD, T. E., RABY, W. T., EPPES, W., HOLBROOK, W. A. and HIGHTOWER, J. A. Aureomycin in treatment of experimental and human tularemia. *J. A. M. A.*, 139: 830-832, 1949.
 22. SELIGMANN, E. and WASSERMANN, M. Action of Chloromycetin on salmonella. *Proc. Soc. Exper. Biol. & Med.*, 71: 253-255, 1949.
 23. SMADEL, J. E., WOODWARD, T. E. and BAILEY, C. A. Relation of relapses in typhoid fever to duration of chloramphenicol treatment. *J. A. M. A.*, 141: 129, 1949.
 24. a. SMADEL, J. E., WOODWARD, T. E., LEY, H. L., JR., PHILIP, C. B., TRAUB, R., LEWTHWAITE, R. and SAVOOR, S. R. Chloromycetin in the treatment of scrub typhus. *Science*, 108: 160-161, 1948. b. SMADEL, J. E., WOODWARD, T. E., LEY, H. L., JR. and LEWTHWAITE, R. Chloramphenicol (Chloromycetin) in the treatment of tsutsugamushi disease (scrub typhus). *J. Clin. Investigation*, 28: 1196, 1949.
 25. GLAZKO, A. J., WOLF, L. M. and DILL, W. A. Tissue distribution, excretion and metabolic fate of chloramphenicol (Chloromycetin). *Federation Proc.*, 8: 57, 1949.
 26. PAYNE, E. H., KNAUDT, J. A. and PALAGIOS, S. Treatment of epidemic typhus with Chloromycetin. *J. Trop. Med.*, 51: 68-71, 1948.
 27. SMADEL, J. E., LEÓN, A. P., LEY, H. L., JR. and VARELA, G. Chloromycetin in the treatment of patients with typhus fever. *Proc. Soc. Exper. Biol. & Med.*, 68: 12-19, 1948.
 28. SMADEL, J. E., TRAUB, R., LEY, H. L., JR., PHILIP, C. B., WOODWARD, T. E. and LEWTHWAITE, R. Chloramphenicol (Chloromycetin) in the chemoprophylaxis of scrub typhus (tsutsugamushi disease). ii. Results with volunteers exposed in hyperendemic areas of scrub typhus. *Am. J. Hyg.*, 50: 75-91, 1949.
 29. SMADEL, J. E., TRAUB, R., FRICK, L. P., DIERCKX, F. H. and BAILEY, C. A. Chloramphenicol (chloromycetin) in the chemoprophylaxis of scrub typhus (tsutsugamushi disease). iii. Suppression of overt disease among volunteers by prophylactic regimens of four weeks duration. (In preparation.)
 30. PINCOFFS, M. C., GUY, E. G., LISTER, L. M., WOODWARD, T. E. and SMADEL, J. E. The treatment of Rocky Mountain spotted fever with Chloromycetin. *Ann. Int. Med.*, 29: 656-663, 1948.
 31. RUMBALL, C. A. and MOORE, L. G. Treatment of a chronic typhoid carrier with Chloromycetin. *Brit. M. J.*, 1: 943, 1949.
 32. KNIGHT, V., McDERMOTT, W. and RUIZ-SANCHEZ, F. Aureomycin and Chloromycetin: use in typhus, typhoid and brucellosis. *J. Clin. Investigation*, (in press), 1949.
 33. MURGATROYD, F. Typhoid treated with Chloromycetin. *Brit. M. J.*, 1: 851-852, 1949.
 34. BRADLEY, W. H. Chloromycetin in typhoid fever. *Lancet*, 1: 869, 1949.
 35. STILLER, R. Typhoid fever treated with Chloromycetin. *J. Pediat.*, 35: 85-87, 1949.
 36. WOODWARD, T. E., SMADEL, J. E., HOLBROOK, W. A. and RABY, W. T. The beneficial effect of Chloromycetin in brucellosis. *J. Clin. Investigation*, 28: 968, 1949.
 37. HARRIS, H. J. Aureomycin and Chloromycetin in brucellosis. *Bull. New York Acad. Med.*, 25: 458-459, 1949.
 38. CHITTENDIN, G. E., SHARP, L. A., GLAZKO, A. J. and SCHILINGMAN, A. S. Chloramphenicol (Chloro-

- mycetin) in therapy of bacillary urinary infection. *J. Clin. Investigation*, (in press), 1949.
39. WOOD, E. J. Atypical pneumonia treated with Chloromycetin. *Lancet*, 2: 55-56, 1949.
40. HORSFALL, F. L., JR. Primary atypical pneumonia. *Viral and Rickettsial Infections of Man*. Chap. 13, ed. 1, pp. 287-294. T. M. RIVERS, Editor. Philadelphia, 1948. Lippincott Company.
41. GREENBLATT, R. B., WAMMOCK, U. S., DIENST, R. B. and WEST, R. M. Chloromycetin in the therapy of granuloma inguinale. *J. M. A. Georgia*, 38: 206-208, 1949.
42. WOODWARD, T. E. Personal communication.
43. ROSE, H. M. and KNEELAND, Y., JR. Aureomycin in the treatment of infectious diseases. *Am. J. Med.*, 7: 532, 1949.

Tetanus Following Dental Extraction^{*}

DWIGHT GRISWOLD, M.D. and ALBERT C. HERRING, M.D.

New York, New York

TETANUS is a rare disease in north-eastern United States. In 1937 Huntington, Thompson and Gordon¹ collected only 642 cases from the records of eighteen hospitals situated in this area. During the peacetime period of 1920 to 1929 the United States Army with an average strength of 130,000 men reported eight cases.² Between 1939 and 1943 there were 3,105 deaths from tetanus in the United States.³ The average annual mortality was 621. At this hospital there have been only five cases in 219,408 admissions during the past twenty-five years. Of the four previous cases two occurred in 1923, one in 1925 and one in 1943. There was one death.

The low incidence of tetanus contributes to the difficulty in diagnosis. Vinnard⁴ reported that in his series of 352 patients treated at the Charity Hospital in New Orleans between 1934 and 1944 twenty-six cases were not diagnosed at first. Of this series fourteen were admitted to the hospital for one to seven days before the correct diagnosis was made.

Following the development of clinical signs of tetanus the prognosis depends on early diagnosis and treatment.⁵⁻⁷ Since the mortality is estimated at between 20 and 50 per cent,^{4,5} the importance of early diagnosis is self-evident.

CASE REPORT

This was the third hospital admission of J. S., a sixty year old colored male complaining of inability to open his mouth, pain in his jaw, back, hips and knees. The past history revealed that he had a primary luetic infection at the age of twenty-six. For the three years previous to

admission he had been treated with bismuth and arsenicals at another institution. Spinal serology was negative in 1932. The patient's first admission was in 1936 with the diagnosis of syphilitic aortitis and mild cardiac decompensation. His second admission occurred in 1937 with the diagnosis of syphilitic aortitis, alveolar abscesses, treatment for an error in refraction and extraction of two teeth. Spinal serology was negative. Since 1937 he had been followed in the cardiac clinic with minimal symptoms and physical findings. In September, 1946, he appeared at the dermatology clinic with a hemostatic ulcer of his left lower leg secondary to varicose veins. By August 1, 1947, it had been considered healed but he was still being treated with 1 per cent ichthyol and Lassar's paste at the time of admission.

Thirteen days before admission the patient had the upper left second molar extracted using novocain anesthesia. Six days before admission he reported not feeling well and complained of a head cold. Four days before admission and nine days following the extraction the patient appeared at the out-patient department complaining he could not talk. His jaw could be opened 1 cm. No tenderness was found on examination. There was no Chvostek sign. Deep reflexes were normal. It was noted that the masseter muscles seemed to go into spasm on attempted opening of the jaw. The patient was seen again that afternoon when it was observed that his jaw appeared swollen about the temporomandibular joint. It was thought that he had a subperiosteal abscess. Surgical consultation was obtained. His temperature was 99.6° orally. There was no local tenderness nor any cervical lymphadenopathy.

Three days before admission and ten days following the dental extraction he returned to the out-patient department where no oral lesion was found to warrant trismus. There were several abrasions of the tongue. Although his

^{*} From the Department of Medicine, St. Lukes Hospital, New York, N. Y.

bite was very powerful, his jaw could be opened wide with a tongue depressor. His condition was considered emotional. Two days before admission he was seen again at the out-patient department. Trismus was still present and poor coordination of his legs was noted. During the three days prior to admission he experienced progressive stiffness of his back and legs, with a developing opisthotonos, constipation and inability to void.

He was admitted by ambulance in severe trismus and extreme opisthotonos. There was no history of convulsions. A tongue depressor could not be forced between his teeth. He experienced difficulty in respiration and breathing was stertorous. There was no history of any cut, puncture wound, splinter or other such portal of entry, nor did physical examination reveal any such evidence. He was admitted with the diagnosis of tetanus. On physical examination the patient was seen to be a fifty year old colored male in acute distress and in severe opisthotonos. Temperature was 99.4°, pulse 80 and respiration 20. He was able to speak only with difficulty and bloody mucus ran from between his teeth. Periodic generalized tonic convulsions, lasting ten to fifteen seconds, began shortly after his admission to the ward. Risus sardonicus was present. Trismus prevented insertion of a tongue depressor blade to open the jaw forcibly more than a $\frac{1}{2}$ cm. By retracting his cheek and inspecting the tongue from the side where his teeth were missing the tongue appeared bloody and lacerated. The site of the dental extraction was poorly visualized because of the trismus and bloody mucus. Forcing the jaw open caused masseter spasm. His neck was rigid and hyperextended. There was no cervical lymphadenopathy. His heart rate was slow and regular. There were no murmurs or enlargement of the heart. On examination of his abdomen there was generalized resistance, and some tenderness was present in the lower aspect of the right rectus muscle. There was stiffness and rigidity of the lower extremities. On passive motion the knee and hip joints could be moved forcibly but incompletely. On the anteromedial aspect of the lower third of the left leg there was a shallow ulcer $\frac{1}{2}$ cm. in diameter with a granulating base. Deep reflexes were 2+ and bilaterally equal and active. Babinski reflexes were negative.

Laboratory data were as follows: Urine analysis revealed a specific gravity of 1.009; albumin,

negative; sugar and microscopic examination, negative. Hemoglobin was 14.9 Gm., 100 per cent, with 9,000 white blood cells, polymorphonuclear cells, 78 per cent, and lymphocytes, 22 per cent. The white blood count rose to 12,900 on his sixth hospital day but then returned to normal. Mazzini and Kolmer tests were 4+ positive. Urea nitrogen was 8.4 mg. per cent; sugar, 96 mg. per cent; calcium, 10 mg. per cent; phosphorus, 3.7 mg. per cent; alkaline phosphatase, 1.3 Bodansky units per cent; total proteins 6.8 Gm. per cent, with the albumin 3.9 Gm. per cent and globulin 2.9 Gm. per cent. The sedimentation rate was 28 mm. on admission, rose to 65 mm. by the nineteenth day and returned to normal at the time of his discharge. Cultures from the dental extraction site and leg ulcer were negative for tetanus bacilli. Spinal fluid was clear; it showed 5 cells per cc., 3 being red blood cells and 2 white blood cells. Spinal fluid protein was 70 mg. per cent. There was no serology report. Guinea pig test for tetanus using the spinal fluid was negative. A chest plate showed slight left ventricular hypertrophy of the heart and a moderately tortuous but not dilated aorta. Electrocardiogram showed normal rhythm, left axis deviation and ventricular ectopic extrasystoles.

A lumbar tap was attempted the night of admission but it was unsuccessful because of extreme opisthotonos. A large pillow was placed under his arched back for support.

He was immediately given tetanus antitoxin 40,000 units intravenously, soluble phenobarbital 4 gr., morphine sulfate $\frac{1}{6}$ gr. and penicillin 30,000 units intramuscularly. Following this he received tetanus antitoxin 40,000 units intravenously every six hours, with soluble phenobarbital 2 gr. every six hours and penicillin 100,000 units intramuscularly every three hours. During this time he was given sedatives to control his spasms but not so deeply as to give him respiratory depression.

On the morning following admission it was noted he was worse. He was unable to talk because of the trismus and sore tongue. A neurosurgical consultation was obtained and a lumbar tap was performed by a lateral approach to the spinal canal. Normal manometrics and clear fluid were found. Tetanus antitoxin 20,000 units were instilled, the only time this route of administration was used. The patient was maintained on parenteral fluids daily: 1,500 cc. 5 per

cent glucose in normal saline, amigen 1,000 cc. and vitamins.

During his first hospital day he experienced several generalized tonic spasms lasting thirty to forty-five seconds and characterized by twitching of the facial and cervical muscles, tightening of the lips, blowing of blood-tinged foam from the mouth and general rigidity. Suction was used at this time since his mouth could be opened about 1 cm.

Neurologic consultation confirmed the diagnosis of tetanus. On surgical consultation it was noted one could get tetanus from a superficial crusted area, but that this patient's leg ulcer was not crusted and thus seemed an unlikely portal of entry. On dental consultation it was noted that the socket appeared to be healing satisfactorily.

By the night of his first day he had received 120,000 units of antitoxin intravenously and 20,000 intrathecally. On the morning of his second day, while trying to void, he experienced tonic contraction of the muscles with increased opisthotonos and generalized rigidity lasting forty-five seconds. He was catheterized and 700 cc. of urine were obtained. By his second day he had shown some improvement. He could open his mouth 1 inch and there was a reduced amount of temperomasseter spasm following forced opening of the mouth. He had a fever of 101°r. during this time. His leg ulcer had healed so that no more than the admission culture was obtained.

By the third day two fingers could be inserted into his mouth. He could talk better and could flex his head slightly on passive motion. The opisthotonos had cleared. At the end of the third day he had received 440,000 units of antitoxin intravenously. By the end of the fourth day this amounted to 520,000 units when the dosage by this route was stopped and he was given 5,000 units intramuscularly daily for only the following three days. By the sixth day he was taking a high caloric fluid diet, he could be gatched up in bed and he could turn himself in bed without assistance. His tongue was treated with gentian violet. On the seventh day he could place his chin within two fingers of his sternum. His main complaint was of a sore tongue.

On his tenth and thirteenth days he received 1,500 units of antitoxin intramuscularly which ended the course of treatment with the antitoxin. With reduction in sedation the patient became more alert on his tenth hospital day. By the

eleventh day his chin could be moved to the sternum and he could feed himself. By the thirteenth day he complained only of weakness and also of continued soreness of his tongue. There was no remaining spasticity of his muscles. Reflexes were physiologic and equal but coordination of the fingers was poor. He was started on physiotherapy. By the fourteenth day he was allowed up progressively. At this time penicillin was stopped. From this point on he showed both subjective and objective improvement. His sedimentation rate reached its maximum level of 65 mm. on the nineteenth day but dropped to 25 mm. at the time of discharge.

His total tetanus antitoxin dosage had been 520,000 units intravenously, 23,000 units intramuscularly and 20,000 intrathecally, an over-all total of 563,000 units. He experienced no serum sickness.

Finally on the thirtieth hospital day he was discharged to the convalescent home.

COMMENTS

Three of Vinnard's fourteen patients admitted to the Charity Hospital were initially diagnosed as cases of hysteria, as was our patient in the clinic. But in hysteria self-traumatization is rarely carried to the point of painful laceration of the tongue.

The history, physical findings and course of our patient leave no doubt as to the diagnosis despite negative cultures. Culturing of the tetanus bacillus is often unsuccessful^{8,9} and negative results do not eliminate the diagnosis; neither does a negative guinea pig test rule out the diagnosis.

The portal of entry presented a peculiar problem. The patient had experienced none of the classical traumas associated with portals of entry. He had had a leg ulcer secondary to varicose veins for thirteen months, but this had been improving under treatment and on admission it appeared as a small, shallow, granulating ulcer which after bed rest and administration of penicillin healed within forty-eight hours. We are left with the history of a dental extraction nine days before the onset of trismus. In our opinion this time relationship is more than a mere coincidence since the incubation period of six to twelve days is the most frequently encountered in tetanus.^{8,10}

Although tetanus following dental extractions is relatively rare, it has been reported. Graves¹⁰ in his report on 813 cases found three following dental extraction. Appleton¹¹ in 1933 found only three other cases reported in the literature.

In this case the portal of entry was the tooth socket. It is interesting on two accounts: First, because such a portal is relatively rare; second, because the fact that there had been an extraction so clouded the clinical picture that the correct diagnosis was delayed.

Treatment was carried out conservatively as outlined in recent papers.^{4-6,12} Tetanus antitoxin was given intravenously every six hours so that by the fourth day he had received 520,000 units. Restlessness and tonic convulsions were adequately controlled by phenobarbital given parenterally. Penicillin was given to ward off secondary infection, particularly hypostatic and aspiration pneumonia, not as therapy specific for the tetanus bacillus. There is controversy as to its specificity, most of the evidence pointing toward its being significant only against secondary infection.^{3,13-15} Supportive measures were also considered important. Parenteral fluids and vitamins were given. He was turned frequently. Constipation and urinary retention were treated.

The patient's respiratory distress was controlled by sedation which never reached the point of danger so that the use of curare was not thought to be warranted.¹⁶⁻¹⁹ In a careful study of the use of curare in tetanus Adriani and Ochsner¹⁷ concluded that the dosage needed to initiate significant muscular relaxation was not adequate until complete curarization was attained. They found that respiratory depression and obstruction were difficult to avoid.

SUMMARY

A case of tetanus is presented. Evidence is given to support the thesis that the site

of a dental extraction was the portal of entry.

Treatment is briefly discussed.

REFERENCES

1. HUNTINGTON, R. W., JR., THOMPSON, W. R. and GORDON, H. H. Treatment of tetanus with antitoxin. *Ann. Surg.*, 105: 93, 1937.
2. KIRK, N. T. Tetanus. Nelson System Surgery. Vol. 1. New York, 1938. Thomas Nelson & Sons.
3. GLENN, F. Tetanus—a preventable disease, including an experience with civilian casualties in the battle for Manila (1945). *Ann. Surg.*, 124: 1030, 1946.
4. VINNARD, R. T. Three hundred fifty-two cases of tetanus. *Surgery*, 18: 482, 1945.
5. RACKEMANN, F. M. Medical progress: allergy serum reactions, with particular reference to methods of prevention and a plan of treatment. *New England J. Med.*, 226: 726, 1942.
6. PRATT, E. L. Clinical tetanus, a study of fifty-six cases with special reference to methods of prevention and a plan for evaluating treatment. *J. A. M. A.*, 129: 1243, 1945.
7. ASHURST, A. P. C. The prognosis of tetanus. *J. A. M. A.*, 87: 2089, 1926.
8. STONE, W. J. and HAMILTON, P. M. Nelson System Medicine. Vol. 1. New York, 1947. Thomas Nelson and Sons.
9. TOPLEY, W. W. C. and WILSON, G. S. The Principles of Bacteriology and Immunity. Pg., 1394. New York, 1937. William Wood & Co.
10. GRAVES, A. M. Tetanus in New Orleans, an analysis of 813 cases. *Ann. Surg.*, 92: 1075, 1930.
11. APPLETON, J. L. T. Bacterial Infection, with Special Reference to Dental Practice. Pg. 35. Philadelphia, 1933. Lea & Febiger.
12. GRAHAM, J. R. and SCOTT, T. McN. Notes on the treatment of tetanus. *New England J. Med.*, 235: 846, 1946.
13. WEINSTEIN, L. and WESSELHOEFT, C. Penicillin in the treatment of tetanus; report of two cases. *New England J. Med.*, 233: 681, 1945.
14. ALTEMEIER, W. A. Penicillin in tetanus. *J. A. M. A.*, 130: 67, 1946.
15. LEWIS, L. Therapeutic trial of penicillin in tetanus. *Ann. Int. Med.*, 25: 903, 1946.
16. SCHLESINGER, E. B. Curare; a review of its therapeutic effects and their physiological bases. *Am. J. Med.*, 1: 518, 1946.
17. ADRIANI, J. and OCHSNER, A. Some observations on the use of curare in the treatment of tetanus. *Surgery*, 22: 509, 1947.
18. CULLEN, S. C. and QUINN, C. S. The use of curare in the treatment of tetanus; case report. *Surgery*, 14: 256, 1943.
19. ISACSON, S. E. and SWENSON, S. A., JR. Curare in the treatment of tetanus; case report. *Nebraska M. J.*, 26: 1136, 1941.

Loeffler's Syndrome with Associated Eosinophilic Polyserositis*

HELEN A. DICKIE, M.D. and ELIZABETH GRIMM, M.D.†

Madison, Wisconsin

Billings, Montana

CASE reports of the syndrome first described by Loeffler in 1932 have been numerous in European but relatively infrequently encountered in the British and American literature. The current concept of the pathogenesis of the syndrome ascribes it to hypersensitivity and suggests that involvement of any tissue may be a feature. Because of the apparent rarity of associated pericarditis with effusion, this case was considered of unusual interest.

CASE REPORT

Mrs. D. S., a thirty-seven year old white married housewife, was admitted to the Wisconsin General Hospital on April 18, 1947, complaining of persistent low grade fever. Her illness had begun during a "flu" epidemic four weeks prior to admission and consisted of fatigue, weakness and anorexia. However, she failed to recover as did the rest of the family and became progressively more dyspneic and orthopneic. She had drenching night sweats and a cough productive of about one-fourth cup of thick white sputum a day. Following a chest roentgenogram on April 7, 1947, she was hospitalized by her local physician and given a course of 1,500,000 units of penicillin. Antihistaminic drugs were also used. In spite of this she did not improve.

Laboratory studies at that time were significant in that with a total count of 11,800 leukocytes there were 30 per cent neutrophils, 28 per cent lymphocytes and 42 per cent eosinophils. The sputum showed no acid-fast bacilli. The Mantoux test was negative. The roentgenogram taken on April 15, 1947, showed progression of the infiltration in the lungs and she was referred

to the Wisconsin General Hospital for further study.

The past medical history included two episodes of fever, cough and other symptoms suggestive of pneumonia. The first occurred at the age of nineteen, shortly after the onset of symptoms diagnosed as "asthma" and necessitated two months of bed rest. The second, at the age of twenty-nine, was more severe and was associated with fever, pleurisy and night sweats. After a chest roentgenogram she was told she had "galloping consumption." However, her sputum was reported to be negative for tubercle bacilli and after three months she recovered completely. She also gave a history of chronic sinusitis, giant urticaria at times and frequent attacks of asthma, some so severe that she required oxygen therapy. She had had nasal polyps removed six or seven times. There was no known contact with tuberculosis.

The family history contributed the fact that her mother had died of Hodgkin's disease (proved by biopsy) and that her two children had asthma and hay fever.

On physical examination she was small, slender, well developed, appeared younger than her stated age and looked chronically ill. The temperature was 99°F., pulse 100 and blood pressure 100/76. Pertinent physical findings were limited to the chest where increased fremitus and breath sounds, and a few post-tussive rales in the right upper chest were noted.

Blood examination showed 12.9 Gm. of hemoglobin with 5,200,000 red cells, 11,400 leukocytes, 37 per cent of which were neutrophils, 16 per cent lymphocytes, 4 per cent monocytes, 40 per cent eosinophils and 3 per cent metamyelocytes. Another leukocyte count showed a total of 11,950 with 45 per cent eosinophils.

* From the Departments of Preventive Medicine and Student Health, and Medicine, University of Wisconsin School of Medicine, Madison, Wis.

† Now associated with the Billings Clinic, Billings, Mont.



FIG. 1. Chest roentgenogram April 19, 1947.



FIG. 2. Chest roentgenogram June 3, 1947.

Her sputum showed no tubercle bacilli or fungi on smear and culture. A skin test was negative with 1 mg. of old tuberculin. Her chest roentgenogram showed the heart size to be normal. (Fig. 1.) There was a distinct thickening of the hilum shadows bilaterally with a nodular appearance on the left. There was coarse, stringy, infiltrative density radiating out from the left hilum into the lung field in the central portion and well marked pleural thickening over the upper lobe. On the right side there was a generalized patchy and conglomerate density scattered throughout the lung field. When compared with previous roentgenograms it was evident that there had been some apical thickening and fibrosis in 1943. The pneumonic process demonstrated in the 1947 films was present chiefly on the right side and underwent considerable fluctuation with regression and recurrence until the last roentgenogram dated April 15, 1947. Since that time there had been clearing of the consolidation but a spread to the right base had occurred.

When studied by the Allergy Department there were no reactions to scratch tests but on intradermal tests there were immediate reactions to grass pollen, feathers, wool, orris root, milk and chocolate, and delayed reactions to tree pollens, ragweed pollen, molds, rabbit hair, house dust, pork and egg. Bacterial vaccines showed large reactions.

It was believed at this time that the patient had Loeffler's pneumonia and she was discharged on April 24, 1947, with the recommendation that contact with the forementioned substances be avoided and desensitization to house dust, bacterial vaccine and co-seasonal pollen be attempted.

The patient was readmitted on May 22, 1947, complaining of pain in the neck, a change in voice and difficulty in swallowing which had developed abruptly one week before. The following day she developed soreness over the precordium and an aching pain in the left arm. Usually the pain was increased on motion and change of position. The pain radiated to her back and at times was so severe that she could be comfortable only when sitting up and leaning forward. She had been conscious of a more rapid heart rate.

The physical examination revealed an anxious but not acutely ill white female who preferred to lie on her left side. The temperature was normal, pulse rate 134 and blood pressure 90/70. The area of cardiac dullness was increased, the heart tones were distant and a pericardial friction rub was heard. There were scattered musical rales throughout the chest. There was epigastric tenderness but the liver edge was not palpated. No paradoxical pulse could be demonstrated.

Again the eosinophiles varied from 20 to 47 per cent in a total of 7,650 to 11,500 leukocytes.

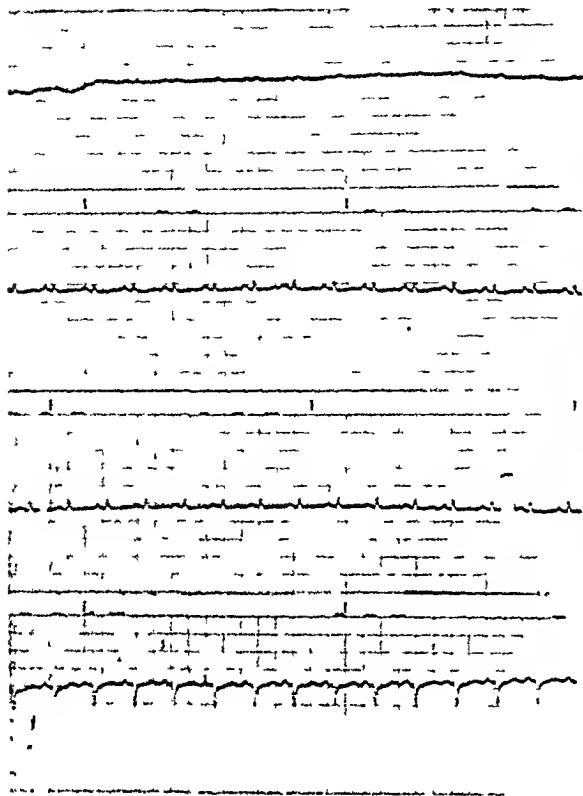


FIG 3 Electrocardiogram

The chest roentgenographic and fluoroscopic examinations confirmed the clinical impression of pericardial effusion. (Fig. 2.) The electrocardiogram was of the pattern noted in pericarditis. (Fig. 3.)

Two diagnostic pericardial aspirations were done and 150 cc. of slightly blood-tinged fluid was removed on each occasion. Of the 3,000 leukocytes per cu. mm. of this fluid, 69 per cent were eosinophiles. The erythrocyte count in the fluid was 71,000 per cu. mm. Cultures of this fluid were negative on aerobic and anaerobic media as well as for tubercle bacilli. Agglutinations for *B. abortus*, *B. tularensis* and *B. typhosus* on this fluid were likewise negative.

A sputum smear showed numerous eosinophiles. A skin test with coccidioidin was negative. The chest roentgenogram showed the cardiac enlargement consistent with pericardial effusion and a small left pleural effusion. At this time the pulmonary parenchyma was essentially normal on the right and considerably less involved on the left than previously.

On the fifteenth hospital day the patient had a sudden sharp pain in the left calf. This was of relatively short duration and she did not report it until the following day. At that time there was



FIG 4. Chest roentgenogram October 6, 1947.

evidence of venous thrombosis with swelling, discoloration and tenderness on pressure over the calf and the inner aspect of the left thigh. She was treated with heparin and then Dicumarol and the symptoms subsided promptly. On discharge from the hospital June 22, 1948, the pericardial friction rub had been absent for several days and the chest roentgenogram showed only slight cardiac enlargement. The pulmonary parenchymal densities had cleared almost completely.

On July 10, 1947, she was seen as an outpatient. Her symptoms were again suggestive of recurrent pericarditis. There was no recognized pericardial rub, but fluoroscopic examination showed increase in the size of the cardiac silhouette consistent with a small pericardial effusion. In the right upper lung field there were scattered densities. The leukocyte count was 12,050 with 20 per cent eosinophiles.

In October, 1947, the patient was seen by Dr. A. M. Olsen of the Mayo Clinic. He wrote that sputum cultures were again negative for tubercle bacilli as well as for pathogenic fungi. Tuberculin, coccidioidin and histoplasmin skin tests were all negative. The chest roentgenogram at that time revealed bilateral upper lung field densities. The cardiac silhouette was larger than on the chest roentgenograms of April, 1947, but was not diagnostic of pericardial effusion (Fig. 4.) The left vocal cord was paralyzed.

Failure to obtain any symptomatic relief from the treatment outlined prompted this patient to go to Arizona. A recent report from the patient's referring physician stated that she had not improved and was bedridden.

COMMENT

This patient had three illnesses which were in all probability recurrent episodes of Loeffler's pneumonia. During the first two experiences complete resolution occurred and no residual pulmonary damage was evident clinically or by roentgen study. In the third episode, the onset was similar and for a period of time the changes were limited to the lungs. The changes were reversible at this time as evidenced by the complete clearing and then recurrence of the parenchymal infiltrates. The serous membrane involvement was evident in the pericardium and pleura. The pericardial effusion subsided. However, because of the subsequent course characterized by continued difficulty in breathing without asthmatic episodes, it is suggested that constrictive pericarditis had developed. Unfortunately, we have not had the opportunity of repeating the examination. The appearance of thrombophlebitis without recognized cause leads to the impression that it was due to vascular damage from the same allergic stimulus. A muscle biopsy was not obtained so that morphologic changes in blood vessels could not be demonstrated.

This patient's course is very similar to that of several others reported by Harkovy. His report deals with sixteen cases, fifteen of which were suffering from typical bronchial asthma. The attacks of asthma were accom-

panied by pulmonary lesions and reactions of serous membranes, including pleura, pericardium and peritoneum. The fluids from these serous cavities were sterile and the eosinophile content was very high. The peripheral blood showed eosinophilia in all cases. Four of the sixteen that came to autopsy were characterized by thickening of the intima of small vessels, necrotizing arteritis, endoarteritis obliterans and fibrosing arteritis in the lungs, serous membranes, myocardium and other organs. The variety of clinical syndromes presented is explained by the number of "shock" tissues that may be involved, either by a reversible or irreversible process. The allergic nature of this patient's illness is suggested by the long history of bronchial asthma, nasal polyposis, urticaria and the allergic state of her two children. The eosinophilia in the peripheral blood and the pericardial fluid is further evidence of the allergic nature of her disease.

CONCLUSION

A case of pneumonia associated with pericardial effusion and venous thrombosis is reported. That the various features of this patient's illness were due to hypersensitivity is supported by the history of bronchial asthma and the discovery of eosinophilia in the blood, sputum and pericardial fluid.

REFERENCES

1. HARKOVY, J. Vascular allergy. Pathogenesis of bronchial asthma with recurrent pulmonary infiltrations and eosinophilic polyserositis. *Arch. Int. Med.*, 67: 709-734, 1941.
2. HARKOVY, J. Vascular allergy. III. *J. Allergy*, 14: 507-537, 1943.

Kala-azar^{*}

With Special Studies of Bone Marrow and Lymph Nodes

WILLIAM J. SENTER, M.D.,

Raleigh, North Carolina

HAROLD SUTKER, M.D. and HORTENSE ELTON GARVER

Atlanta, Georgia

KALA-AZAR (visceral leishmaniasis) is a tropical disease that was rarely seen in this country before World War II, only eight cases having been reported in the United States.¹⁻⁸ It has been estimated by Most⁹ that fifty to seventy-five cases occurred in American personnel during the recent war. Many more cases may manifest themselves during the next few years. The disease should be of interest to physicians who care for veterans, particularly as there is available specific therapy which dramatically alters the high mortality rate of untreated patients.

This report presents an instance of kala-azar in a veteran of the North African, Sicilian and Italian campaigns. He had been treated as a case of malaria for over two years before the proper diagnosis was established. A detailed study of bone marrow biopsy is included to demonstrate the high incidence of parasitized cells in the reticuloendothelial system and to emphasize the diagnostic value of this procedure.

CASE REPORT

W. A. N., a twenty-eight year old white male, a World War II veteran, was admitted to the Lawson Veterans Administration Hospital on October 27, 1947, complaining of fever, weakness, distention of the abdomen and weight loss of 25 pounds. In July, 1944, while in Southern Italy, he developed generalized aching, chills, fever and headaches. He was admitted to an Army hospital where malarial parasites were said to have been found on blood smear and

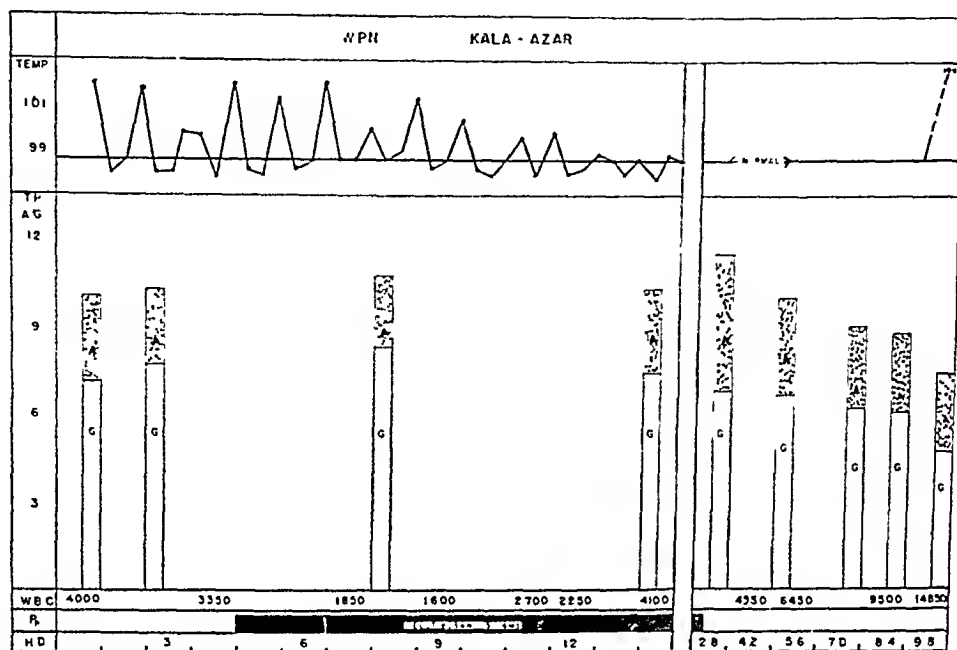
quinine therapy was instituted. His symptoms improved and after eight days he was discharged. Two weeks later he returned to the hospital with similar complaints. Although repeated examinations for malarial parasites were negative, he was given antimalarial therapy and improved again, but he continued to run a low grade fever after returning to duty. In July, 1945, there was a mild reappearance of symptoms that did not require treatment or hospitalization. He was returned to the United States in August of that year and was separated from the service. Episodes of malaise, generalized aching, chills and fever occurred in November, 1945, November, 1946, March, 1947 and June, 1947. On two occasions he received further antimalarial therapy although malarial parasites were not demonstrated. During the two years before admission he had noted progressive weakness and weight loss although he maintained a fairly good appetite in periods of remission. He first noted dyspnea, pedal edema and brownish discoloration of the skin (forehead and face) in October, 1946. Several months before admission a physician told him he had an enlarged spleen.

The patient appeared chronically ill, with evidence of marked weight loss. The abdomen was markedly protuberant. The temperature was 101°F., pulse 100, respirations 20, and blood pressure 130 mm. of mercury systolic and 80 mm. diastolic. A diffuse brownish pigmentation of the forehead and face was noted. There was discrete generalized lymphadenopathy. The liver and spleen were greatly enlarged, firm but non-tender, and there was flaring of the costal margins. The over-all liver dullness in the mid-clavicular line measured 25 cm., the splenic dullness in the anterior axillary line

^{*} From the Medical Service, Lawson Veterans Administration Hospital, and the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

Laboratory data were as follows: The red blood cell count was 3.1 million per cu. mm. and the blood hemoglobin concentration was

The urinalysis showed a specific gravity of 1.021, negative tests for sugar and albumin and a rare white blood cell in the urinary sediment. Stool specimens contained *Hymenolopsis nana*



8.2 Gm. per 100 cc. The packed red cell volume was 30 per cent, the mean corpuscular volume 96 cubic micra, mean corpuscular hemoglobin 26 micro micrograms and mean corpuscular hemoglobin concentration 27.3 per cent. The reticulocyte count was 4.4 per cent. Examination of the blood smear showed excessive rouleaux formation, anisocytosis and poikilocytosis. The white blood cell count was 4,000 per cu. mm., with a differential count of 35 per cent metamyelocytes, 31 segmented neutrophils, 29 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. Subsequent blood counts showed from 3,000 to 4,000 white blood cells with 2 to 8 per cent plasma cells. The coagulation and bleeding times were normal and the prothrombin time matched the normal control diluted to 30 per cent with physiologic saline. The blood sedimentation rate was 29 mm. in one hour (Wintrobe). The blood Kahn was negative. Serum agglutination studies for typhoid "O" and "H," paratyphoid "A" and "B," brucella, heterophils antibody and *Proteus* OX-19 were negative. Blood chemistry analyses included a markedly positive formol gel reaction, total serum protein of 9.8 Gm. per 100 cc. with 7.4 Gm. of globulin and 2.4 Gm. of albumin. The thymol turbidity reaction

In February, 1948, the patient was re-admitted with uncomplicated pneumococcal lobar pneumonia. At that time the pigmentation on his face and forehead had cleared completely. The liver and spleen had returned to normal size and he had gained 25 pounds in weight. It

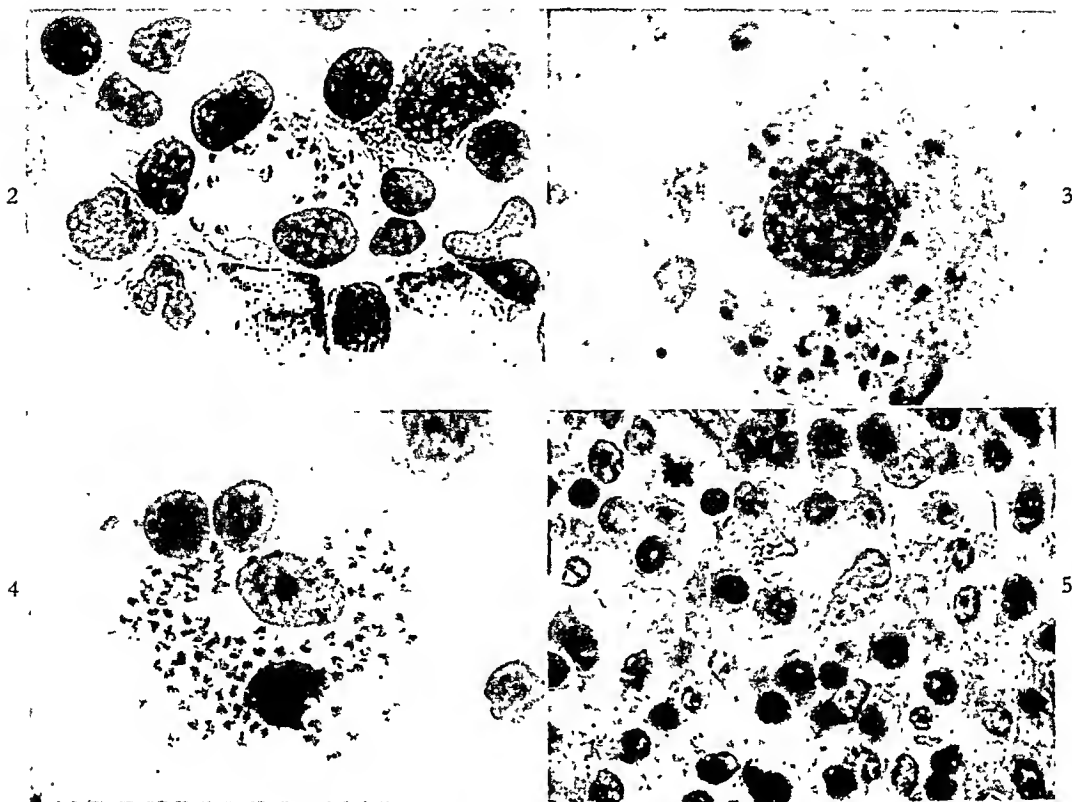


FIG. 2. Wright's stained serum spread of bone marrow showing *Leishmania donovani* engulfed by a macrophage.

FIG. 3. Higher magnification of macrophage in bone marrow containing *Leishmania donovani*. With Wright's stain the parasites show pale blue cytoplasm, dark purple nucleus and brilliant dot-like kinetoplast. Two extracellular parasites appear at upper left.

FIG. 4. Wright's stained serum spread of lymph node showing macrophage filled with parasites.

FIG. 5. Histologic section of lymph node stained with phyloxine-methylene blue showing parasites appearing as inclusion bodies in the cytoplasm of a macrophage.

is of interest to note that he had a leukocytosis of 14,650 on this admission. He was discharged asymptomatic and appeared entirely recovered when last seen in April, 1948.

Sternal bone marrow was obtained by surgical trephine and aspiration and two lymph nodes were removed from the epitrochlear region. Serum spreads were prepared from small portions of the curetted marrow and stained with Wright's stain, Giesma and Papanicolaou's stain. Numerous *Leishmania donovani* were demonstrated in the cytoplasm of macrophages, metamyelocytes and occasionally in segmented neutrophils in all preparations. (Figs. 2 and 3.) It is estimated from the differential and total cell counts¹⁰ shown in Table I that 22,560 parasitized cells were present per cu. mm. of marrow. Smears made from heparinized blood aspirated from the marrow showed only a rare parasitized cell. Many parasites were found extracellularly appearing as small "torpedo" forms. Serum spreads, made from scrapings of the cut surface of the lymph node and stained with

Wright's stain, revealed many parasitized macrophages.

Histologic preparations of bone marrow and lymph node were fixed in Zenker's solution with 5 per cent acetic acid and stained with phyloxine methylene blue. In the preparations the parasites appeared much smaller than in serum spreads of the bone marrow but could be recognized under oil immersion as small dot-like inclusion bodies in the cytoplasm of macrophages. (Figs. 4 and 5.) The bone marrow showed generalized hyperplasia of both myeloid and erythroid elements. The megakaryocytes were markedly increased but only a few appeared to be producing platelets. This finding has been described by Cartwright.¹¹ The most striking abnormality was the large number of plasma cells (15.8 per cent) and parasitized macrophages (3.2 per cent). It is interesting that more neutrophils were parasitized than macrophages, but in the former the morphology of the parasite was distorted. The differential bone marrow count is shown in Table I.

TABLE I
HEMATOLOGIC FINDINGS IN BONE MARROW

	Curretted Marrow	Heparin-ized Sinusoidal Blood
	per cu. mm.	per cu. mm.
Total nucleated cell count	705,000	14,000
Myeloid leukocytes	305,970	
Nucleated erythrocytes	177,660	
Macrophages and monocytes	56,400	
Plasma cells	111,390	
Lymphocytes	38,775	
Megakaryocytes	14,805	
	705,000	
Macrophages containing parasites	22,560	
Neutrophils containing parasites	31,020	
Reticulocytes, per cent	14	
Erythroid-myeloid ratio	1 to 1:7	

	No.	Per cent	Total per cent
Differential cell count (1,000 cells):			
Reticulum cells	32	3.2	
Myeloblasts	34	3.4	
Promyelocytes	59	5.9	
Neutrophilic myelocytes	75	7.5	
Eosinophilic myelocytes	14	1.4	
Neutrophilic juveniles (16 parasitized)	114	11.4	
Neutrophilic bands (22 parasitized)	64	6.4	
Neutrophilic segmenters (6 parasitized)	32	3.2	
Eosinophils	10	1.0	43.4
Monocytes	14	1.4	
Macrophages (32 parasitized)	66	6.6	8.0
Pronormoblasts	4	0.4	
Basophilic normoblasts	83	8.3	
Polychromatophilic normoblasts	139	13.9	
Orthochromic normoblasts	26	2.6	25.2
Plasma cells	158	15.8	15.8
Lymphocytes	55	5.5	5.5
Megakaryocytes	21	2.1	2.1
Totals	1,000 cells	100.0	100.0

The architecture of the lymph node had been largely destroyed and in the section studied

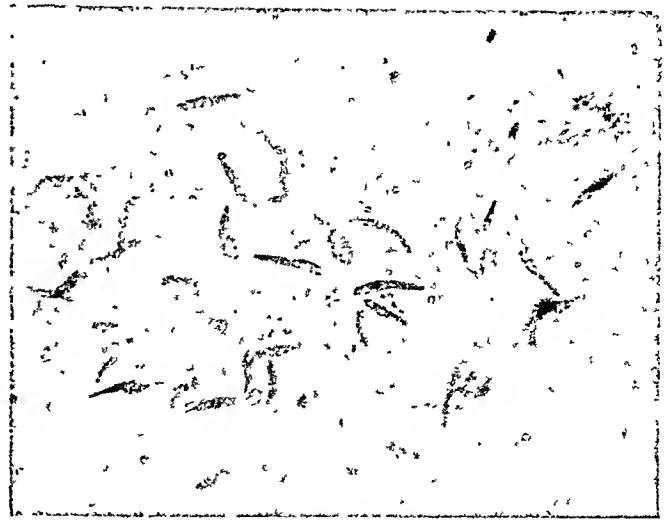


FIG. 6. Motile, flagellated forms of the parasite stained with brilliant cresyl blue from fourteen-day culture on NNN medium.

only one small germinal center could be identified. Numerous plasma cells were present in the medullary cords and there were many large mononuclear macrophages containing an abundant eosinophilic cytoplasm. Within the cytoplasm of these cells small basophilic inclusion bodies, surrounded by a clear zone, were identified.

Smears of leukocytic cream were examined and an extremely rare parasite was found in the cytoplasm of segmented neutrophils.

Cultures on Nicolle-Novy-MacNeal medium¹ were made from the button of bone marrow, curretted marrow, heparinized sinusoidal blood, a macerated lymph node and peripheral blood drawn immediately following biopsy. Leptomenas forms were demonstrated in all cultures from the tenth to the fourteenth day, with the exception of peripheral blood cultures which remained sterile. (Fig. 6.)

COMMENT

Kala-azar is prevalent throughout the world's tropical and sub-tropical zones but is most common along the Mediterranean Sea, Central Africa, India, Burma and China. The etiologic agent is *Leishmania donovani*, a paratozoal organism of the family trypanosomidae. This organism can be cultured on NNN medium and grows as a flagellated protozoa. In the cells of the reticuloendothelial system, however, it appears as a round, ovoid body measuring 2 to 5 micra in diameter.

The phlebotomus sandfly is generally considered to be the vector of kala-azar. The incubation period varies from a few

days to eighteen months.¹² The characteristics of the disease are chills, fever, generalized malaise, pigmentation of the skin, enlargement of the liver and spleen, and progressive loss of weight. The principal laboratory findings are leukopenia and hyperglobulinemia. The disease is most frequently confused with malaria. The high remittent fever and splenic enlargement common to malaria and kala-azar may make a differential diagnosis difficult. Many patients suffering from kala-azar have received antimalarial treatment on a purely empiric basis.

The diagnosis of kala-azar may be confirmed by the demonstration of the organism in bone marrow or lymph nodes by smear, culture or hamster inoculation. Splenic puncture¹³ is commonly employed in many countries, but is not recommended because of the hazards involved.^{14,15} The rapid formol gel reaction is not diagnostic of kala-azar but is an indication of hyperglobulinemia which is characteristic of the disease. It is of interest that the spinal fluid in this case showed no elevation of total protein.

Our bone marrow studies conform with those of Cartwright, Chung and Chang,¹¹ and those of Rachmilewitz, Braun and DeVries.¹⁶ The high degree of parasitization of bone marrow cells is especially striking.

It is noted that the laboratory findings of hyperglobulinemia, plasmacytosis of the bone marrow and excessive rouleau formation, considered characteristic of multiple myeloma, are found consistently in kala-azar. This coincidence of findings is the rationale for the treatment of multiple myeloma with stilbamidine as recently reported by Snapper.¹⁷

It is quite possible that many cases of kala-azar will be found in veterans who served in endemic areas. Confirmatory laboratory tests are not beyond the scope of most clinical laboratories. Once the diagnosis of kala-azar is proven, the results of therapy are gratifying and the prognosis changes from a mortality of 90 to 95 per cent without treatment to 2 to 5 per cent with specific antimony compounds.

SUMMARY

This report presents an instance of kala-azar occurring in a veteran of the North African, Sicilian and Italian campaigns. He had been treated as a case of malaria for over two years before the proper diagnosis was established. A detailed study of a bone marrow biopsy is included to demonstrate the high incidence of parasitized cells in the reticuloendothelial system and to emphasize the diagnostic value of this procedure.

REFERENCES

1. MUNTER, E. J. and PACKCHANIAN, A. Two exogenous cases of visceral leishmaniasis (kala-azar) in the United States with notes on cultivation of *Leishmania donovani* in vitro. *Am. J. Trop. Med.*, 25: 507, 1945.
2. MATHIESON, D. R. and WATSON, B. A. Kala-azar. *J. A. M. A.*, 112: 308, 1939.
3. ROSE, R. M. Cold hemagglutinins in visceral leishmaniasis (kala-azar). *Proc. Soc. Exper. Biol. & Med.*, 58: 93, 1945.
4. Proceedings of 1944 Seminar, American Society of Clinical Pathologists, Army Institute of Pathology, pp. 85 and 87.
5. PRICE, F. L. and MAYER, R. A. A case of Kala-azar. *J. A. M. A.*, 125: 490, 1944.
6. SWEENEY, J. S., FRIEDLANDER, R. D. and QUEEN, F. B. Kala-azar simulating splenic anemia. *J. A. M. A.*, 128: 1020, 1945.
7. KAMINSKY, F. and WEVER, G. K. Visceral leishmaniasis. *New York State J. Med.*, 46: 522, 1946.
8. BURCHENAL, J. H. and WOODS, R. P. Visceral leishmaniasis. *War Med.*, 7: 173, 1945.
9. MOST, H. and LAVIETES, P. H. Kala-azar in American military personnel. *Medicine*, 26: 221, 1947.
10. ISAACS, R. The bone marrow in anemia. *Am. J. M. Sc.*, 193: 181, 1937.
11. CARTWRIGHT, E., CHUNG, H. L. and CHANG, A. Studies on the pancytopenia of kala-azar. *Blood*, 3: 249, 1948.
12. LEVY, M. D., JR. and YIENGST, S. C. Kala-azar: report of a case showing unusual leukocyte response and prolonged incubation period. *J. A. M. A.*, 136: 81, 1948.
13. NAPIER, L. E., SEN GUPTA, P. C. and SEN, G. N. The treatment of kala-azar by diamidino stilbene: analysis of 101 cases. *Indian M. Gaz.*, 77: 321, 1942.
14. SCOVEL, F. G. Kala-azar: a review of its incidence and epidemiology in China and clinical observations of 585 cases. *Ann. Int. Med.*, 21: 607, 1944.
15. ECKER, H. D. and LUBITZ, J. M. Kala-azar in the United States; review of literature and report of two cases; stilbamidine treatment. *Ann. Int. Med.*, 26: 720, 1947.
16. RACHMILEWITZ, M., BRAUN, K. and DE VRIES, A. Hematologic observations in a case of kala-azar. *Blood*, 2: 381, 1947.
17. SNAPPER, I. Stilbamidine and pentamidine in multiple myeloma. *J. A. M. A.*, 133: 157, 1947.

Editorial

Infectious Mononucleosis

FOR the third time in this century infectious mononucleosis is enjoying a new peak of attention. It is convenient to divide the history of infectious mononucleosis into four periods. The first period was that of clinical description which opened in 1885 and ended with the discovery of the blood changes in 1920. The second period, dominated by the hematologists, lasted from 1920 to 1932 and it was during this time that infectious mononucleosis emerged as a clinical entity through the unification of at least three poorly defined and independent clinical pictures. Pediatricians recognized glandular fever, otolaryngorhinologists described monocytic angina and other forms of throat infection associated with changes in the lymphocytes, and internists knew of severe febrile illnesses with changes in the lymphatic system and in the blood which at times simulated fatal clinical pictures. These three disease groups were found to have an abnormal blood picture in common and studies of this culminated in the classic description of the hematology of infectious mononucleosis by Downey¹ in 1923. By the end of the hematologic period infectious mononucleosis had been firmly established as a clinical entity. The third, or serologic period, started in 1932 when Paul and Bunnell² were surprised to find sheep cell

agglutinins in the serum of a patient with infectious mononucleosis. This additional laboratory method, available both for diagnosis and investigation, led to the extensive serologic studies that characterized the third period. In spite of the detailed descriptions of the blood cell morphology and growing utilization of the serologic reactions the problems of epidemiology, etiology, pathology and therapy remained unsolved. One difficulty was a lack of adequate knowledge regarding the pathology of infectious mononucleosis. The fourth period, that of pathologic description, opened in 1944. Since then pathologists have made three major reports based upon excellent autopsy studies. The publications of Ziegler,³ Allen and Kellner,⁴ and Custer and Smith⁵ are based upon a total of ten autopsies. We now know that infectious mononucleosis is a generalized disease and that there are infiltrations of abnormal lymphocytes in almost every organ of the body.

The pathology of infectious mononucleosis is now clear. The basic lesion is a perivascular infiltration of both normal and abnormal lymphocytes which Custer and Smith⁵ found in all tissues that they studied except the bone marrow. They believe these cells to be metaplastic and to be formed *in situ* from other cells of the reticulo-endo-

¹ DOWNEY, H. Acute lymphadenosis compared with acute lymphatic leukemia. II. Hematologic studies. *Arch. Int. Med.*, 32: 82, 1923.

² PAUL, J. R. and BUNNELL, W. W. The presence of heterophile antibodies in infectious mononucleosis. *Am. J. M. Sc.*, 183: 90, 1932.

³ ZIEGLER, E. E. Infectious mononucleosis; report of a fatal case with autopsy. *Arch. Path.*, 37: 196, 1944.

⁴ ALLEN, F. H., JR. and KELLNER, A. Infectious mononucleosis; an autopsy report. *Am. J. Path.*, 23: 463, 1947.

⁵ CUSTER, R. P. and SMITH, E. B. The pathology of infectious mononucleosis. *Blood*, 3: 830, 1948.

thelial system. The cells are not considered invasive. The lesion may persist long after the patient is judged to be well.⁴ This fundamental and characteristic lesion is not at all uniform in its distribution throughout the body, and in any individual patient may be most marked in the central nervous system, liver or lungs. The myocardial lesions which have been seen are rarely severe enough to cause more than transient electrocardiographic abnormalities; the renal infiltrations produce an interstitial nephritis but are not known to cause permanent disability. Alarming symptoms occur when the infectious mononucleosis infiltration is predominant in the central nervous system, and under these circumstances the clinical pictures of benign lymphocytic meningitis, encephalitis or the Guillain-Barré syndrome may be produced. Two fatal instances of the Guillain-Barré syndrome caused by infectious mononucleosis have been studied both by Custer and Smith⁵ and by Ricker, Blumberg, Peters and Widemann.^{6,7} When the infectious mononucleosis lesion is marked in the lungs, the clinical and x-ray pictures are those of primary atypical pneumonia. Both the clinical pictures and the pathologic lesions of infectious hepatitis and infectious mononucleosis with severe hepatitis can hardly be distinguished. Numerous studies of liver function have established that almost every patient who is ill enough to come to the attention of a physician has some degree of impairment of liver function.^{8,9} Watson and his co-workers⁹ have just reported their studies upon twenty-five patients with in-

fectious mononucleosis and find a significant increase in the total urinary coproporphyrin excretion. The increase is usually found in association with other evidence of functional impairment of the liver. The splenic lesion is characteristic, with lymphocytic infiltration and thinning of the capsule and dissolution of the trabeculae. Smith and Custer¹⁰ describe this as a weakening of the basic structure of the spleen. The expanding splenic volume together with the structural weakness is dangerous and leads to occasional spontaneous rupture in the third week of the disease.

Infectious mononucleosis is one of the acute reticulo-endothelioses; almost certainly infectious in nature and, from the immunologic pattern, it is an infection that could hardly be bacterial in nature. So far, transmission experiments both with experimental animals and human volunteers have given conflicting results. The etiologic agent has not been identified.

The serologic mechanisms associated with infectious mononucleosis and with the sheep cell agglutinins usually demonstrable at some stage of the disease remain obscure. The antibody present in the serum of patients with infectious mononucleosis is not a true Forssman heterophile antibody.¹¹ Recent work by Schwarzweiss and Tomcsik,¹² based upon the demonstration by Stuart and his co-workers^{13,14} of a thermostable heterogenetic antigen in beef erythrocytes, has resulted in the isolation of a heterogenetic "mononucleosis antigen" from the

⁴ RICKER, W., BLUMBERG, A., PETERS, C. H. and WIDEMAN, A. The association of the Guillain-Barré syndrome with infectious mononucleosis. *Blood*, 2: 217, 1947.

⁵ PETERS, C. H., WIDEMAN, A., BLUMBERG, A. and RICKER, W. A. Neurologic manifestations of infectious mononucleosis, with special reference to the Guillain-Barré syndrome. *Arch. Int. Med.*, 80: 366, 1947.

⁶ BROWN, J. W., SIMS, J. LER., WHITE, E. and CLIFFORD, J. E. Liver function during infectious mononucleosis. *Am. J. Med.*, 6: 321, 1949.

⁹ WATSON, C. J., HAWKINS, V., CAPPS, R. B. and RAPAPORT, E. M. Studies of coproporphyrin. IV. The per diem excretion and isomer distribution in the urine in infectious hepatitis, infectious mononucleosis and mechanical jaundice. *J. Clin. Investigation*, 28: 621, 1949.

¹⁰ SMITH, E. B. and CUSTER, R. P. Rupture of the spleen in infectious mononucleosis. *Blood*, 1: 317, 1946.

¹¹ BAILEY, G. H. and RAFFEL, S. Hemolytic antibodies for sheep and ox erythrocytes in infectious mononucleosis. *J. Clin. Investigation*, 24: 288, 1935.

¹² SCHWARZWEISS, H. and TOMCSIK, J. Isolation of the heterogenetic "mononucleosis antigen" from the stroma of beef erythrocytes. *Proc. Soc. Exper. Biol. & Med.*, 69: 558, 1948.

¹³ STUART, C. A., GRIFFIN, A. M., FULTON, M. and ANDERSON, E. G. E. The nature of the antibodies for sheep cells in infectious mononucleosis. *Proc. Soc. Exper. Biol. & Med.*, 34: 209, 1936.

¹⁴ STUART, C. A., GRIFFIN, A. M., WHEELER, K. M. and BATTEY, S. A thermostable antigen in beef-cells. *Proc. Soc. Exper. Biol. & Med.*, 34: 212, 1936.

stroma of beef erythrocytes.¹⁵ This antigen which is alcohol-soluble and heat-stable resists digestion by pepsin and inhibits the sheep cell agglutination by infectious mononucleosis serum in dilutions as great as 1:2,400,000. It can be separated from the serum sickness antigen also present in beef red blood cells.¹⁶ This significant advance may, in time, improve our understanding of the Paul-Bunnell test.

Hitherto the disease has been underestimated, both in regard to its total effect upon young population groups and in its potential harm to the individual patient. Physicians who deal with military and student populations are well aware of the significant amount of lost time. Even when the disease is mild there are frequently prolonged periods of disability. The incidence seems to be increasing, perhaps as a result of increasing population density and of the population shifts of World War II. A similar increase in frequency occurred in England and in the United States following World War I.

Serologic and hematologic surveys made during epidemics have indicated that there may well be an enormous number of sub-clinical infections underlying the visible epidemiologic pattern of infectious mononucleosis. A carrier state is not impossible. As with diseases known to be caused by viruses, it is possible that infectious mononucleosis changes its character from time to time. Thus in the British epidemic of 1930 almost every patient had a skin rash but

jaundice was not recorded. By 1935 to 1936 the picture had changed in England; the rash was seen less frequently and jaundice was relatively common. The hepatic, pulmonary and central nervous system manifestations of infectious mononucleosis, which are so evident at this time, may represent other changes in the potentialities of the unknown infectious agent. The evident danger to the community and to the individual makes necessary a more energetic attack upon the problems of etiology and forces us to consider the public health aspects more closely.

The treatment of infectious mononucleosis remains symptomatic and unsatisfactory. Bower^{17,18} has had excellent therapeutic response in patients who were given gamma globulin. Evans¹⁹ has recently reported a two-fold increase in the beta and gamma globulin of the blood in patients convalescent from infectious mononucleosis. Both of these observations will undoubtedly receive considerable further study. Patients should have some type of dietary management for their ever present hepatitis. When the disease has been marked by jaundice, it is probable that physical activity should be controlled during convalescence as it is with infectious hepatitis.

Infectious mononucleosis is no longer properly regarded as a diagnostic curiosity or as a benign and unimportant disorder. The disease always impairs vital organs, frequently incapacitates and occasionally kills.

GEORGE H. HOUCK, M.D.

¹⁵ SCHWARZWEISS, H. and TOMCSIK, J. Über das physikalisch-chemische Verhalten der Antigen in Hammelblutstromata. *Schweiz. Arch. f. Path. u. Bakt.*, 11: 446, 1948.

¹⁶ TOMCSIK, J. and SCHWARZWEISS, H. Nature of the heterogenetic hapten reacting with hemagglutinins in horse serum sickness. *Proc. Soc. Exper. Biol. & Med.*, 69: 562, 1948.

¹⁷ BOWER, A. G. Infectious mononucleosis. *Arizona Med.*, 6: 17, 1949.

¹⁸ BOWER, A. G., AFFELDT, J. E. and WEST, H. The treatment of the anginose type of infectious mononucleosis with gamma globulin. *J. Pediat.*, 35: 58, 1949.

¹⁹ EVANS, A. S. Liver involvement in infectious mononucleosis. *J. Clin. Investigation*, 27: 106, 1948.

Radioiodotherapeusis*

ROBERT H WILLIAMS, M.D., BEVERLY T. TOWERY, M.D.,† HERBERT JAFFE, Ph.D.,
Seattle, Washington *Nashville, Tennessee* *New York, New York*

WALTER F. ROGERS, JR., M.D. and RENE TAGNON, M.D.
Syracuse, New York *Boston, Massachusetts*

THE reports of other investigators^{1,2} indicate that radioactive iodine can be used effectively in the treatment of thyrotoxicosis. In most of the early studies radioiodine with a half-life of twelve hours (I^{130}) was used but with the availa-

had no evidence of thyrotoxicosis at the time of radioiodotherapeusis; three had non-toxic nodular goiter and two had malignant adenoma.

Of the ninety-seven patients who received I^{131} , ninety-three (Table II) had previously

TABLE I
TYPE OF 111 PATIENTS TREATED

Disease	No of Patients
Thyrotoxicosis	106
Non-toxic nodular goiter	3
Malignant adenoma	2

bility at low cost of isotope with a half-life of eight days (I^{131}) from Oak Ridge, Tennessee, the use of the latter has become more practical. We have treated 111 patients with radioiodine, chiefly I^{131} , and are reporting our results in this paper. Many factors concerned in the effectiveness of radioiodotherapeusis and the selection of optimal doses are discussed in the succeeding paper.³

TYPES OF PATIENTS TREATED

With the exception of one subject with a thymergastic reaction all of the thyrotoxic individuals who sought treatment during the period from December, 1946, to December, 1947, were treated with radioiodine. As shown in Table I there were 106 of these. Three received I^{130} and 103 received I^{131} . In six of the 103 patients treatment was begun only in the last three months so they are omitted from discussion. Five patients

TABLE II
PREVIOUS TREATMENT OF NINETY-SEVEN PATIENTS

	No
Subtotal thyroidectomy	21
Thiouracil* treatment	93
0-4 months	35
4-8 months	18
8-16 months	30
16-24 months	10

* The term "thiouracil" is used to include not only the parent compound but also its derivatives. With few exceptions, however, it refers to 2-thiouracil and 6-n-propylthiouracil.

been treated with one of the thiouracils; fifty-six of these had received such therapy for four months or longer. However, radioiodine was never given immediately after a long course of one of the thiouracils. Some of the patients had had serious toxic reactions to thiouracils and a few had had untoward reactions to iodide. Twenty-one had undergone one or more subtotal thyroidectomies;† further operative care would have been difficult in a few individuals.

Of the seventy-six individuals not previ-

† In the presentation of data we have considered in a separate class patients who had been previously thyroidectomized because of greater difficulties in evaluating the characteristics of the thyroid glands and because of a possible difference in their response.

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass., and from the Department of Medicine, University of Washington, Seattle, Wash.

† Research Fellow aided by the Commonwealth Fund.

ously operated upon twenty-two had a nodular goiter* and fifty-four had diffuse hyperplasia of the thyroid. There were essentially the same number of cases with mild, moderate and severe disease. (Table III.) The ages of the patients (Table IV)

TABLE III
SEVERITY OF THYROTOXICOSIS

	No.
Mild.....	32
Moderate.....	33
Severe.....	32

ranged from fifteen to seventy years. There were twice as many females as males.

At the time radioiodine was given several of the patients had congestive heart failure, one was suffering from acute glomerular nephritis and another had chronic pyelonephritis. Three individuals had had acute hepatitis within a few months prior to therapy. One patient received a single dose of I^{131} during the first two months of her pregnancy.

PLAN OF THERAPY

Before each patient was given radioiodine the degree of thyrotoxicity was evaluated clinically and by means of determinations of the basal metabolic rate. Special attention was given to the type and duration of previous therapy and to the size,† configuration and consistency of the thyroid. The characteristics of the gland together with the clinical status of the patient proved ultimately to be the most useful criteria in selecting the initial dose of radioiodine and in establishing the need for subsequent administration of isotope.

All I^{131} was obtained from Oak Ridge and the radioactivity of the isotope at the time of its administration was based upon the standards of the laboratories‡ which

* We apply the term "nodular goiter" only when we are of the impression that circumscribed nodules are present.

† Upon each visit of the patient specific estimation was made of the size of the gland. It is believed that satisfactory evaluations can be made in most of the patients when the gland is less than approximately 70 Gm. (see Appendix).

‡ The Clinton Laboratories of the Monsanto Chemical Co., Oak Ridge, Tenn.

provided the isotope. Prior to its ingestion by the patient the stock solution was diluted with distilled water so that 10 ml. contained 1 mc.* In the majority of patients 0.3 to 0.5 mg. of potassium iodide was employed as a carrier. On eleven occasions 50 mg. of

TABLE IV
AGE AND SEX DISTRIBUTION OF NINETY-SEVEN PATIENTS

Age Decade	No. of Patients
11-20.	5
21-30. . .	21
31-40.	19
41-50.	23
51-60. . .	20
61-70.	9
Male. . . .	33
Female. . .	64

this compound were given; fifteen patients received 2 Gm. of sodium bromide with the I^{131} .

Of course, the selection of dosage was the greatest problem; many aspects of this are presented in the succeeding paper.³ Initially we attempted to ascertain how much of the radioiodine was stored in the thyroid gland following tracer (100 μ c) or therapeutic doses. Among the methods used were epithyroid counts; early, medium and late changes in the total and protein-bound radioiodine concentration of the serum; urine excretion studies and combinations of these. However, we soon found, as presented in the next paper,³ that none of these methods was a very accurate indicator of the dosage that would be required ultimately. Early we adopted the policy, which was explained to each patient, that it was much easier to give one or more additional doses than to treat a myxedematous state that might result from larger doses. Therefore, we attempted to give the very minimal

* Upon arrival of a consignment of I^{131} , usually 75 to 100 mc., it was moved promptly to a special laboratory where the dilution was accomplished with minimal exposure. The stock solution was kept in an enclosure of two-inch lead bricks. Essentially all of the isotope was dispensed on the day of its arrival and the return of the patients to widely separated communities lessened the concentration of radioactive material in a confined region. Dental roentgen-film badges were worn by all personnel who worked with the stock solution. Random monitory counts throughout the laboratory showed minimal contamination.

TABLE V
ADJUNCTIVE THERAPY

Treatment	No. of Patients		No. of Treatments
	No Treatment	Treatment	
Thiouracil Pre-I*	24	73	112
KI Carrier	3	94	199
KI Post-I*	46	51	77

* This therapy was given for a few weeks preceding the radioiodotherapeusis, usually being discontinued three or four days before the latter. It is not to be confused with the thiouracil therapy given for four months or longer to fifty-six patients. The latter was discontinued at least one month before the isotope treatment.

quantity which we decided might be necessary. In most patients the initial dose was from 3 to 7 mc.

In our initial experiences with radioiodotherapeusis it was found that three patients who were treated with nothing but radioiodine experienced an exacerbation in thyrotoxicity of the nature of a thyroid storm. This was prevented in subsequent patients by using propylthiouracil, usually from 200 to 300 mg. daily, for a few weeks before the radioiodine, discontinuing its use approximately four days before the latter. In many cases additional aid was afforded by the administration of potassium iodide, 3 drops twice daily for five days, beginning the day after the radioiodine. In Table v is presented the number of times

TABLE VI
EFFECT OF DURATION OF PREVIOUS TREATMENT WITH THIOURACILS UPON DOSAGE OF RADIOIODINE REQUIRED TO PRODUCE REMISSION WITHIN SIX MONTHS IN PATIENTS WITH DIFFUSELY HYPERPLASTIC GOITERS
(NONE HAD BEEN OPERATED UPON)

Thiouracils (months administered)		0	0-4	4-8	8-16	16-24
Total mc.	R	6-11 3	4.5-16	5-12	3 5-16 5	2-11
	M	8 4	9.1	8.4	7 1	6 4
	SD	2 6	4.2	2 1	3.5	3 9
Number of doses	R	1-3	1-4	1-3	1-4	1-2
	M	1 7	2 3	1 7	1 7	1 5
	SD	1 0	0.9	0 7	0 3	0 2
μ C/Gm. thyroid	R	150-177	112-400	155-300	133-366	66-275
	M	164	251	233	221	174
	SD	13 5	93 5	57 2	81 4	91 2
μ C./Gm. thyroid/month *	R	75-88	56-100	50-150	45-125	33-71
	M	82	82	86	76	56
	SD	6 6	13 2	34 5	22.2	17 7
μ C./Gm. combined weights of thyroid *	R	150-177	182-266	120-280	100-200	120-170
	M	164	210	172	149	145
	SD	13 5	29.0	64 8	43.3	35.4
Months before remission	R	1-2	2-6	1-3	1-4	1-5
	M	1 7	3 3	2 3	2 3	2 2
	SD	0 6	1 0	0 9	1 5	1 9
No. of Patients		3	12	8	15	4

R = range

M = median

SD = standard deviation

* For a discussion of these calculations, see footnote in text. In calculating μ C./Gm. thyroid/month only the quantity of isotope used per month in the first six months was included.

that propylthiouracil and potassium iodide were used in conjunction with the radioiodine therapy.

Six patients were hospitalized at the time radioiodine was given; the remainder were followed quite satisfactorily through their periodic visits to the laboratory. Ordinarily patients were seen during the first week

month the patients were seen once a month and at bimonthly intervals thereafter. It was necessary to follow some patients much more closely than this.

RESULTS OF THERAPY

Ninety-two of ninety-seven thyrotoxic patients treated with I^{131} experienced a

TABLE VII

COMPARISON OF DOSAGES OF RADIOIODINE USED TO PRODUCE REMISSION IN SIX MONTHS IN PATIENTS PREVIOUSLY TREATED WITH THIOURACILS FOR LESS THAN FOUR MONTHS* WITH THOSE REQUIRED FOR PATIENTS WHO HAD NODULAR GOITER OR WHO HAD PREVIOUSLY HAD THYROIDECTOMY

Group		Diffuse Goiter	Thyroidectomy Previously	Nodular Goiter
Total dose mc.	R M SD	4.5-16 9.1 4.21	4-11 7.7 2.38	4-36 14.7 11.3
Number doses	R M SD	1-4 2.3 0.9	1-2 1.5 0.17	2-5 2.4 1.5
$\mu\text{c./Gm. thyroid}$	R M SD	112-400 251 93.5	133-296 197 58.9	160-319 216 59.9
$\mu\text{c./Gm. thyroid/month}^\dagger$	R M SD	56-100 82 13.2	34-125 73 34.3	40-100 66 18.8
$\mu\text{c./Gm. combined weights of thyroid}^\dagger$	R M SD	166-230 210 29	88-153 110 29.4	89-131 115 15.4
Months before remission	R M SD	2-6 3.3 0.96	1-4 2.0 1.17	1-5 3.3 1.6
No. of patients		12	8	13

R = range

M = median

SD = standard deviation

* Only those patients treated with thiouracil for less than four months are included in this analysis; treatment for longer intervals is more likely to influence the results.

† For a discussion of these calculations, see footnote in text.

after receiving the isotope and then at intervals of two weeks throughout the first two and a half months. Up to the sixth

TABLE VIII
DURATION OF SUSTAINED REMISSIONS

Months	Diffuse Hyperplasia	Thyroidectomy	Nodular Goiter
1-4	7	..	4
4-7	6	2	1
7-10	24	7	10
10-13	14	9	3
13-16	3	2	..

sustained remission* of thyrotoxicosis; mild hyperthyroidism persisted in five; persistent myxedema developed in three.

I. Sustained Remissions. 1. *Interval Preceding Onset; Duration:* In eighty-three subjects (86 per cent) remissions with sustained euthyroidism were observed within six months following initial therapy with radioiodine. Six patients who exhibited evidences of thyrotoxicosis six months after their initial treatment subsequently became euthyroid. The duration of previous thiouracil therapy had no significant effect upon the promptness of those responses which occurred within the six-month period in patients with diffuse hyperplastic goiters. (Table VI.) The median values of the duration of the intervals between the initial I^{131} treatment and the establishment of remissions in patients treated with thiouracil for less than four months were as follows: 3.3 months in patients with diffusely hyperplastic goiters; and 2.0 months in patients who had previously undergone thyroidectomy. (Table VII.) Although the response to radioiodine was somewhat more prompt in the last group, the differences are not statistically significant. The duration of remissions thus

* "Sustained remission" is applied to patients who have become euthyroid and have remained so for more than one month.

far is shown in Table VIII. The degree of permanency of the remissions must await more prolonged observations. One of the five patients who did not have a remission disappeared from observation after only one dose had been given. Some additional data

TABLE IX
TOTAL NUMBER OF DOSES OF RADIOIODINE

No. Doses	No. of Patients with Sustained Remission	No. of Patients without Sustained Remission
1	32	1
2	28	..
3	21	1
4	7	..
5	3	1
6	..	2
7	1	..

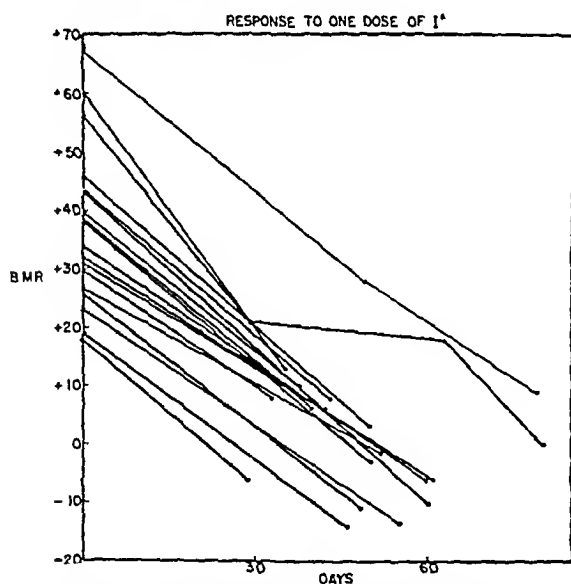


FIG. 1. None of the patients included in this plot had received radioiodine previously. Each individual experienced a remission following one dose of the isotope which has been maintained subsequently; none developed myxedema.

in the case are given in Figure 6 of the succeeding paper.³ The thyroid glands of each of the other four have decreased to a normal or subnormal size and it is believed that none will require more than a small amount of additional therapy, if any.

2. *Dosage of Radioiodine:* A total of 222 doses was given to ninety-seven patients, an average of 2.2 doses per subject. (Table IX.)

In thirty-two individuals only one dose, 2 to 8 mc. was required to produce a sustained remission, the average being 5.3 mc. The decrease in the basal metabolic rate in a representative group of these patients is shown in Figure 1. Some individuals re-

TABLE X
TOTAL DOSAGE OF RADIOIODINE ADMINISTERED BEFORE SUSTAINED REMISSION OCCURRED

Total Dosage mc.	No. of Patients with Sustained Remission		
	Within Six Months	After Six Months	None
2	1		
3	2		
4	11	1	
5	9		
6	10		
7	9	..	1
8	5		
9	6		
10	5	1	
11	6		
12	3	..	1
13	4		
14	2	2	
15	2	1	
16	2		
18	..	1	1
20	1	1	
21	..	1	1
25	2	1	
27	1
30	1		
36	2		

quired several doses before a remission was produced. (Fig. 2.)

As shown in Table VI and discussed in the following paper,³ the duration of previous therapy with thiouracil did not exert a statistically significant effect on the quantity of radioiodine required; however, experiences with individual patients make us entertain the possibility. This group of patients was given an average of approximately 8 mc. divided into two doses. Patients who had been previously thyroidectomized also required approximately 8 mc.

The largest doses were given to the twenty-two subjects with toxic nodular goiters; each individual received an average

of about 14 mc. Each of two such patients was given a total of 36 mc. divided in the manner indicated in Figure 3. Doses equal to twice the amount needed to produce myxedema in some patients with diffuse toxic goiter were tolerated with relative impunity in certain subjects with toxic nodular goiter. Some of the patients were much more refractory than others (Table x) irrespective of whether the gland was nodular; fourteen required more than three doses and one required seven. As discussed in the next paper, many factors are concerned in determining the dosage of radioiodine required. Two important factors are the characteristics of the thyroid gland and the interval between treatments.* These factors are partially considered in Tables vi and vii. Approximately 225 μ c. of radioiodine per Gm. of thyroid weight was required to produce remission. When calculated in the manner described in the foot-

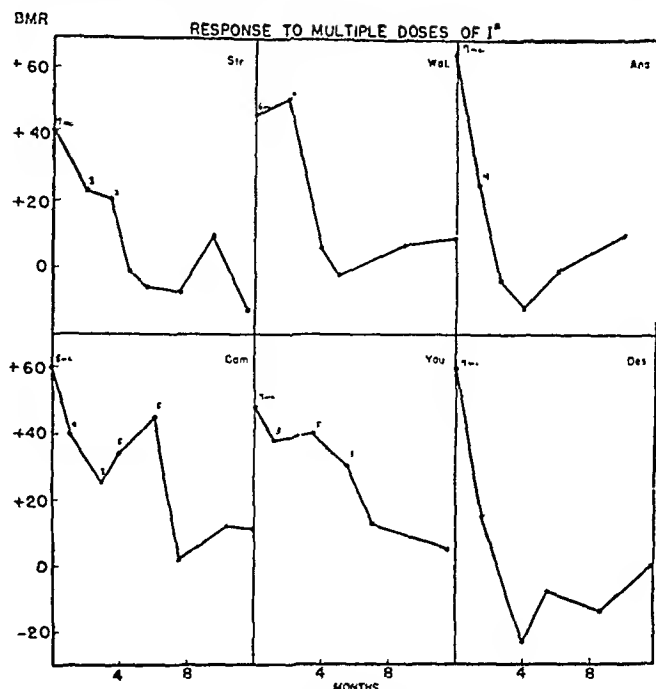


FIG. 2. The small numerals indicate the number of millicuries of radioiodine administered. Note that the decrease in basal metabolic rate was fairly precipitous once an adequate dose had been given.

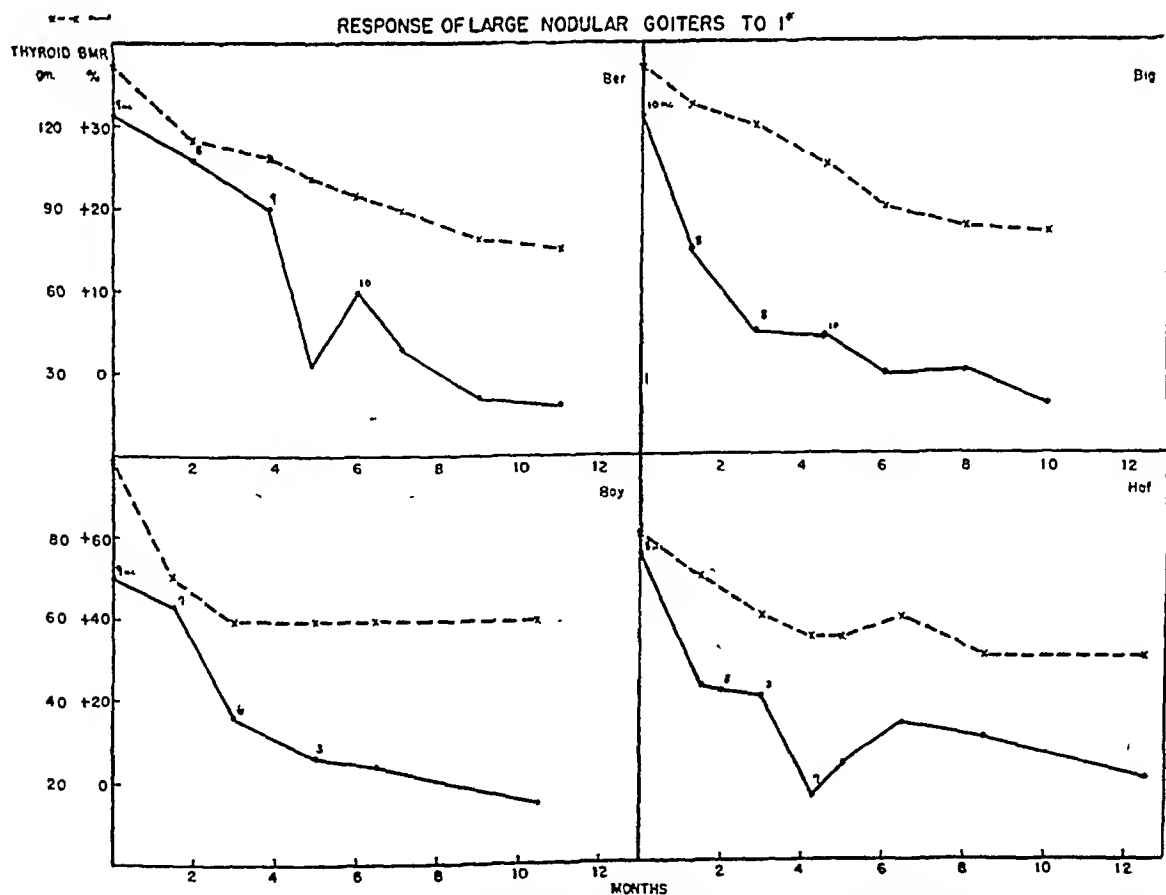


FIG. 3. Note that a large amount of radioiodine was required before these patients with large nodular goiter experienced a remission of their thyrotoxicity. In each case the size of the goiter decreased to some extent and thereafter showed little change in spite of the large doses of radioiodine. It may be observed that patient Big. received 18 mc. after reaching a state of euthyroidism, without significant effect upon the metabolic rate.

note* around 75 $\mu\text{c.}/\text{Gm.}$ thyroid/month was used. The patients with diffuse goiter required more $\mu\text{c.}/\text{Gm.}$ of combined weights of thyroid (Tables VI and VII) than did those with nodular goiter and the patients who had been thyroidectomized previously.

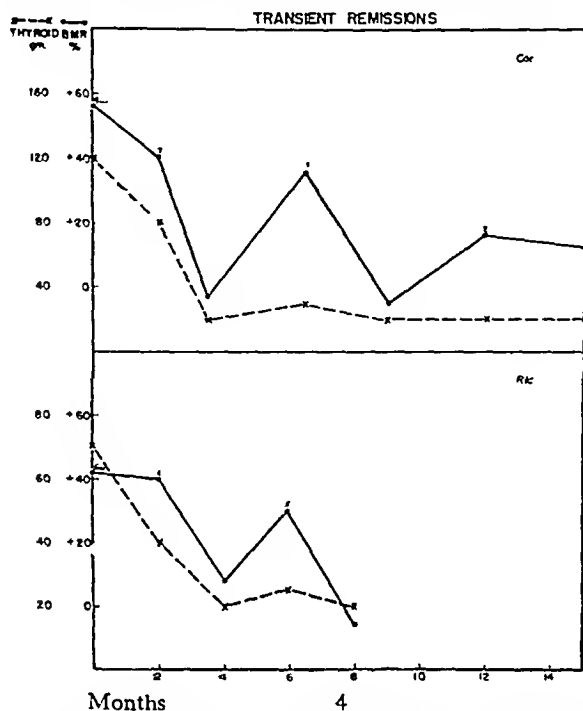
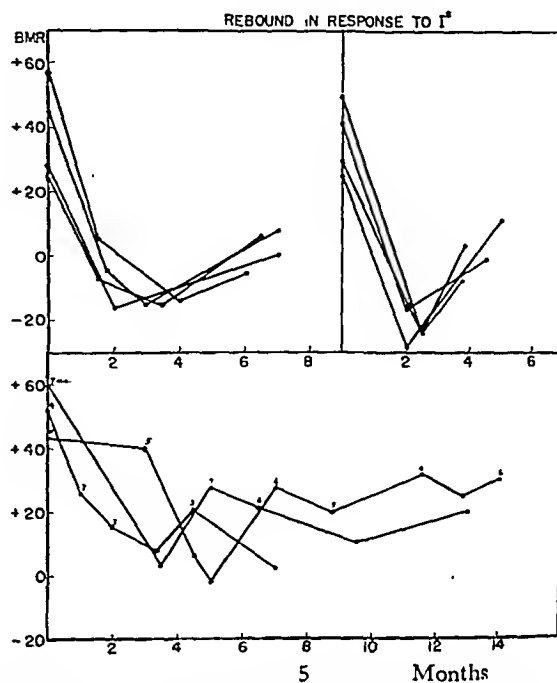


FIG. 4. Note the marked decrease in the size of the goiters. With the relapses in thyrotoxicity only slight increases in thyroid size occurred. Note that the second and third remissions occurred with successively smaller doses; this, however, has not been true in certain other cases.

FIG. 5. In the two top charts the subnormal response in metabolic rate in eight patients is shown. The maximal decrease occurred between two and four months after radioiodotherapy; within approximately six months the range had become normal. None of these patients has developed thyrotoxicosis subsequently. The lower graph demonstrates how the metabolic rate may be temporarily normal but increase thereafter to a degree sufficient to require more therapy.

in Figures 4 and 5. It can be observed in one instance (Fig. 5) that there was a transient remission after 10 mc. were administered but 17 mc. given in the next seven months failed to produce another remission. On the other hand, one patient (Fig. 4) experi-



II. Complete Transient Remissions and Transient Hypothyroidism. Some of the patients developed complete remissions that were only of short duration as exemplified by the response in the basal metabolic rate, shown

* The following example is given as an indication for considering the amount of treatment given per month. A patient with a gland weighing 50 Gm. might experience a remission if 8 mc. were given as an initial dose, whereas thyrotoxicity would be likely to persist if 4 mc. were given initially and 4 mc. two months later. Thus the time factor must be considered. Since it takes about two months or longer for the maximal clinical effect to be exerted, we have empirically used this interval for convenience as the average interval needed for evaluating the action of each dose. Most of the injurious effect of the isotope would occur in the first four weeks. However, additional time is required for the inactivation of hormone that had been manufactured previously.

The patient, mentioned above, who was given 8 mc.

enced his first remission after 11 mc., the second after 5 mc. and the third after 2 mc. A third subject (Fig. 4) experienced no response after 5 mc. but a short remission was induced after an additional 4 mc.

in one dose received 80 $\mu\text{c.}/\text{Gm.}/\text{mo.}$; if given 4 mc. in each of two doses he would have received 40 $\mu\text{c.}/\text{Gm.}/\text{mo.}$ Since this calculation fails to take into consideration the amount of decrease in the size of the gland which occurred between the first and second treatments, another calculation was made, $\mu\text{c. I}^*/\text{Gm.}$ "combined" thyroid weight. Applying this calculation to the above example, the two doses would be added together and the initial thyroid weight would be added to the weight estimated immediately preceding the second dose. If the latter was 30 Gm., by dividing the sum of the millicuries by the sum of thyroid weights, the average $\mu\text{c. I}^*/\text{Gm.}$ combined thyroid weight (or average thyroid weight) is obtained. In addition to the foregoing calculations the $\mu\text{c. I}^*/\text{Gm.}$ of thyroid was determined for each dose.

Following 5 mc. the patient developed a complete remission which has persisted for eight months.

As a consequence of treatment with I^{131} one patient developed transient hypothyroidism which, however, was of such long duration as to merit further discussion:

This patient (*Lac.*) first began treatment of moderately severe thyrotoxicosis in 1944 at the age of twenty-seven. She took thiouracil continuously for nine months but promptly relapsed after cessation of therapy. Thiouracil therapy was again instituted for a period of ten months and again there was a reappearance of thyrotoxicosis after the drug was withdrawn and the BMR rose to plus 20 per cent. The estimated weight of the thyroid at this time was approximately 25 Gm. The patient was given 4 mc. of I^{131} under these circumstances; two months thereafter the BMR was minus 13 and one month later was minus 29. The patient took desiccated thyroid intermittently throughout the next eight months. She has now received no thyroid medication for four months, is clinically in a euthyroid state and the metabolic rate is minus 9 per cent. She is in the third month of pregnancy.

There were fifteen other patients who developed significant temporary hypothyroidism which lasted for one to six months. Five of them were given desiccated thyroid for intervals of two to eight weeks but it has not been necessary for any of them to take this therapy for the last three months, with the exception of one patient with severe acute pituitarigenic ophthalmopathy. The latter patient did not have evidence of myxedema while not receiving thyroid for six weeks.

III. Complications of Therapy. 1. Persistent Myxedema: Only three patients developed lasting myxedema subsequent to the administration of I^{131} . As this constituted the only significant complication of such therapy, the pertinent points in each case are given in some detail:

Patient Sa.: When first seen in 1943 this man, aged fifty-two, had severe thyrotoxicosis with a goiter estimated as weighing 60 Gm. He was treated continuously with thiouracil for nineteen months and after the first month remained

in remission throughout this period. However, by the sixteenth month of therapy the goiter had increased to 130 Gm.; during an interval of three months, 2,000 roentgen units were given over each lobe of the thyroid and the gland decreased to about 90 Gm. Thereafter he received several courses of therapy in the following order: methylthiouracil, potassium iodide, butylthiouracil and propylthiouracil. Therapy was interrupted after each course and thyrotoxicosis reappeared within a few weeks. Thirty months after the completion of roentgen therapy the thyroid had decreased to a weight of about 35 Gm., but three months after the cessation of all antithyroid therapy the metabolic rate was plus 43 per cent. At this time he was given 5 mc. of I^{131} with 0.3 mg. of potassium iodide and no other therapy. Two months later the BMR was minus 10 per cent; a month thereafter, minus 3 per cent and six months after receiving I^{131} it had fallen to minus 44 per cent. At this time no thyroid tissue was palpable and the patient presented a clinical picture typical of myxedema. During the past six months he has required continuous therapy with desiccated thyroid.

Patient Buc.: A female patient, aged twenty-seven, was found to have thyrotoxicosis in 1934 and therapy with thiouracil was instituted and continued for a period of eighteen months; during the last seventeen months of this period she was free of thyrotoxicosis. However, two months after the cessation of therapy thyrotoxicosis recurred. Thiouracil treatment was resumed for a period of three months and subtotal thyroidectomy was performed. Eleven months later there was a return of symptoms of hyperthyroidism and the basal metabolic rate was found to be plus 19 per cent. At this time she was given 5 mc. of radioactive iodine. Within six weeks the goiter and evidences of thyrotoxicosis disappeared and the basal metabolic rate was minus 14 per cent; within four months the patient became typically myxedematous and the metabolic rate had fallen to minus 35 per cent. Replacement therapy with desiccated thyroid was begun and has been continued to date, a period of about six months.

Patient Cl.: A housewife, aged thirty-four, had had a subtotal thyroidectomy in 1934 at the age of thirty-one. In 1944 thyrotoxicosis reappeared and she was treated with thiouracil for a period of nine months but a relapse followed cessation of therapy. Potassium iodide was then given for a period of six months but failed to control her disease and was supplanted by

propylthiouracil for a period of fourteen months. Withdrawal of the latter therapy was followed by a recrudescence of thyrotoxicosis and the basal metabolic rate rose to plus 23 per cent, although the estimated weight of the thyroid was only 15 Gm. At this time the patient re-

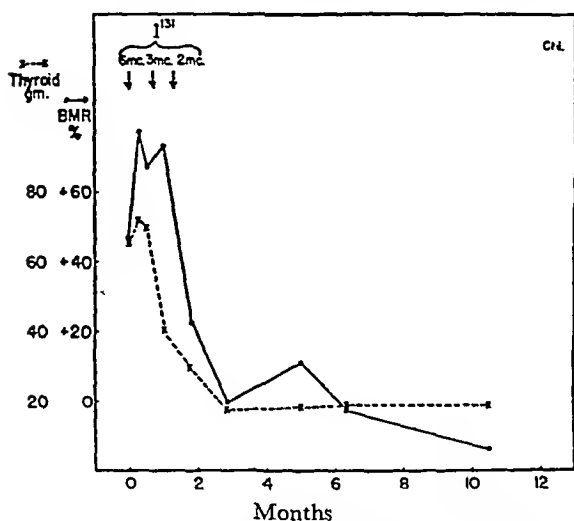


FIG. 6. Note the increase in the metabolic rate and gland size following radioiodine. The decrease in gland size preceded the decrease in metabolic rate. This patient received no specific therapy before or after the radioiodine.

ceived 4 mc. of I^{131} . Seven weeks thereafter the pulse rate was 120 per minute, there was a moderate amount of sweating and tremor and the metabolic rate was plus 19 per cent; an additional 3 mc. of radioiodine were given at this time. Two months after the second dose of I^{131} overt myxedema was apparent and the basal metabolic rate was minus 27 per cent. To date the patient has been maintained on desiccated thyroid for a period of eight months.

The complications in the foregoing three patients were encountered relatively early in this study and occurred among patients who had previously been subjected to prolonged antithyroid therapy, thyroidectomy or roentgen therapy or a combination thereof. Under these circumstances it is frequently difficult to ascertain the requisite dose of isotope and subsequent experience suggests the use of relatively small doses in the treatment of patients who have had prolonged antithyroid therapy or in whom only a slight regrowth of tissue has occurred after thyroidectomy. Therefore, in the treatment of patients similar to Sa. and Buc., an

initial dose of 3 to 4 mc. is now preferred over the 5 mc. which both individuals received. However, it must be emphasized that other patients with very similar clinical courses received as much or more therapy without the development of persistent myxedema. It appears quite likely that Cl. received the second dose of I^{131} prematurely; an interval of at least ten weeks after the initial dose would have afforded a greater margin of safety.

It is noteworthy that eight of the patients who developed transient hypothyroidism and two of those who developed myxedema had previously experienced subtotal thyroidectomy for the removal of a diffusely hyperplastic thyroid. On the other hand, no patient with a nodular goiter developed transient hypothyroidism or myxedema.

2. Immediate Undesirable Effects: During the first five days after the administration of I^{131} an occasional patient complained of mild headache, anorexia, nausea and malaise. These symptoms apparently did not depend upon the effects of radioiodine upon the thyroid. Among the patients whose thyrotoxicosis was associated with congestive heart failure, acute glomerular nephritis or chronic pyelonephritis there were no ill effects related to the complicating disease. The three patients who had had severe hepatitis apparently suffered no deleterious effects from I^{131} and the woman who received radioiodine during the first two months of pregnancy gave birth to a normal baby.

Three patients developed a very distinct, and several others a milder, exacerbation in the severity of thyrotoxicosis within the first week after the administration of I^{131} . The more severe reaction may be illustrated by the following case:

A Chinese girl, aged twenty-three, had moderately severe thyrotoxicosis and the diffusely enlarged thyroid weighed approximately 65 Gm. The basal metabolic rate was plus 48 per cent and, without antecedent therapy, she was given 6 mc. of I^{131} . On the third day she complained of pain and increased fullness in the region of the thyroid; by the sixth day, a marked increase in



FIG. 7. Note the marked decrease in the fullness of the neck. Only 4.5 mc. were required to produce a remission of thyrotoxicity and to reduce the thyroid to a size estimated as 10 gm.; it had been 50 gm. Overcompensated hyperphagia accounted for the slight obesity observed in the photograph on the left.

restlessness, tremor, sweating and tachycardia was noted. At this time it was quite obvious that there had been a distinct increase in the size of the thyroid and the basal metabolic rate was found to be plus 70 per cent. (Fig. 6.) At no time had there been clinical or bacteriologic evidence of acute infection. Following this acute exacerbation there was rapid improvement and decrease in the size of the thyroid; three weeks after the administration of the initial dose of I^{131} the weight of the thyroid was approximately 40 Gm. Subsequently three and two millicurie doses of I^{131} were given; the thyroid ultimately returned to normal size and the patient has remained free of thyrotoxicosis for a period of eleven months.

IV. Changes in the Thyroid Gland. 1. *Diffuse Thyroid Hyperplasia:* Except for the single patient who disappeared from observation, the thyroid decreased to an estimated weight of 25 Gm. or less in all individuals with diffuse goiter who received I^{131} . (Table xi.) The goiter usually regressed more rapidly than did clinical evidences of thyrotoxicosis which often persisted for a considerable time after the thyroid had assumed normal physical characteristics. Figure 7 illustrates the effects of I^{131} in decreasing the size of exophthalmic goiter in one individual; the most marked regression was noted in one patient whose estimated thyroid weight decreased from 120 to 20 Gm.

TABLE XI
SIZE OF THYROID GLAND BEFORE AND AFTER
RADIOIODOTHERAPEUSIS

Grams	Diffuse Hyperplasia		Thyroidectomy		Nodular Goiter	
	Be-fore	After	Be-fore	After	Be-fore	After
20	.	26	1	11	..	3
20-30	9	27	9	10	2	7
30-40	21	..	7	..	3	4
40-50	15	..	2	..	5	2
50-60	4	1	4
60-70	3	.	1	..	2	1
70-80	2	2	1
80-100	1	..	4	
100 or more	4	

These anatomic and metabolic effects of radioiodine are apparently produced by destruction of large masses of cells by radioiodine. During this study no attempt was made to investigate the morphologic changes in the thyroid immediately after the administration of I^{131} . However, it was possible to obtain sections of the thyroid in two patients who were euthyroid as a result of such therapy. Figure 8 shows the thyroid morphology two months after the administration of a single dose of 8 mc. of I^{131} . Figure 9 illustrates the changes in the gland



FIG. 8. A and B, Section of thyroid from a patient (Si.) who had had severe thyrotoxicosis. Before any radioiodine was given the gland was estimated as weighing 45 gm. and the basal metabolism rate was plus 70 per cent. Two months following the administration of 8 mc. of radioiodine clinical evidence of thyrotoxicity disappeared, the metabolic rate became normal and the gland decreased to 20 gm. At this time and without further preparation the anterior half of the lateral lobes of the thyroid gland and all of the isthmus were extirpated; the tissue removed weighed 12 gm. The patient has remained euthyroid for the subsequent six months. Note that only a relatively small amount of scar tissue is present and that all of the acinar cells appear active. The magnification in A is 400 X; in B 800 X.

FIG. 9. A and B, Naz. had severe thyrotoxicosis and 60 gm. of thyroid tissue. Several determinations showed the basal metabolic rate to be approximately plus 100 per cent. She was given 18 mc. of radioiodine in three doses within seven months. A state of euthyroidism was obtained within three months following the last treatment. The thyroid gland decreased to an estimated weight of 15 gm. At operation what appeared to be approximately one-half of the gland was removed; the tissue weighed 6 gm. Thus the gland had decreased to 25 per cent of its original size. The fibrous tissue, indicated by the black bands, encircles nests of hyperplastic acinar cells. Presumably large sheets of cells were destroyed in certain areas whereas the cells that remained viable continued to be active. The magnification in A was 100 X and in B 800 X.

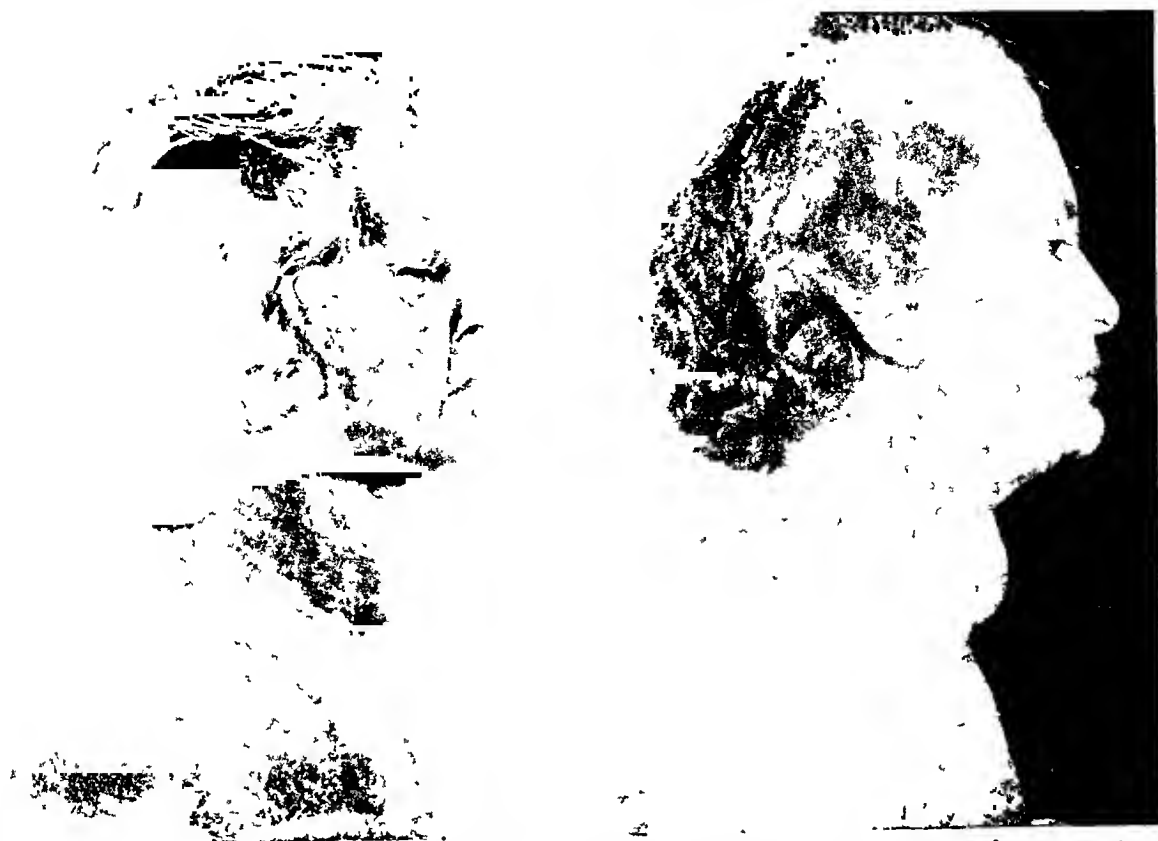


FIG. 10. Bcr. was a female clerk, aged fifty-one, who had been known to have a goiter for twenty-two years. For several months she had had severe compression of the trachea associated with suffocating spells. Subtotal thyroidectomy was recommended but refused by the patient. After treatment with propylthiouracil for several weeks radioiodotherapy was given. (Fig. 3.) Following administration of 26 mc. of radioiodine a complete remission of thyrotoxicosis occurred and the pressure symptoms disappeared. The thyroid gland was estimated to weigh 140 gm. before therapy and 70 gm. thereafter; the measurements decreased from 7 by 6.5 cm. to 5 by 4.5 cm. The changes in the general appearance of the neck are shown in this illustration. An additional 10 mc. of radioiodine did not have very much effect on the basal metabolic rate nor the size of the goiter.

which were found after three doses of radioiodine; tissue was removed ten months after the initial therapy or three months subsequent to the third and last dose of I^{131} . A comparison of Figure 8 with Figure 9 reveals the greater degree of interstitial fibrosis in the latter. It is probable that the differences are related to the larger dose of I^{131} therapy in the latter. It is quite apparent that at this stage the evidence for loss of functioning thyroid cells is largely inferential; the cells which remain reveal no detectable abnormality under the microscope. It should be noted that partial thyroidectomy after I^{131} therapy offered no particular technical difficulty although a few adhesions were encountered between the thyroid and the adjacent tissues.

2. *Toxic Nodular Goiter*: Judging from the anatomic characteristics of such goiters it is not surprising that I^{131} frequently failed

to bring about a reduction of the gland to normal size. Remaining relatively unaffected was that portion of the goiter made up of scar tissue and large colloid follicles or cysts. Although the hyperfunctioning adenomatous tissue might be markedly reduced, the remaining inert constituents persisted with little or no regression even though a euthyroid state had been achieved by radioactive iodine.

Figure 10 shows the changes which were produced in such a goiter by the repeated administration of I^{131} for a total dose of 36 mc. The thyroid, although still large, was reduced from *circa* 140 to 70 Gm. and symptoms of tracheal compression disappeared. Radioiodine was utilized only as a last resort in the treatment of this individual who steadfastly refused operation. It should be emphasized that the cosmetic results of I^{131} therapy are much less satisfactory for

toxic nodular than for diffusely hyperplastic goiters.

V. Treatment of Thyrotoxicosis with I^{130} . Only three patients were treated with radioiodine bearing a half-life of twelve hours (I^{130}). In each of these individuals the results were excellent as indicated by the following abstracts:

Wi., aged fifty-one, a female patient with thyrotoxicosis of moderate severity, after having failed to maintain a remission upon cessation of thiouracil therapy at the end of one year was given 30 mc. of radioiodine. Within three months her thyroid gland decreased from 50 to 20 Gm. and the thyrotoxicity disappeared. She has maintained a remission for two years.

Fe., a tailor, aged seventy-two, with severe thyrotoxicosis, after having responded with toxic reactions to orthophenylene thiourea and thio-barbital (?) and after insufficient improvement with propylthiouracil, was given 25 mc. of radioiodine. Within three months the thyroid gland decreased from 40 to 20 Gm. and the thyrotoxicosis subsided. He has maintained this remission for eighteen months.

Ru., a housewife, aged forty-nine, had moderately severe thyrotoxicosis. Within six months following 25 mc. of radioiodine the thyroid decreased from 30 to 20 Gm. and a remission of the disease was initiated; it has been maintained for eighteen months.

VI. Non-toxic Nodular Goiter. In an attempt to decrease the size of such goiters three individuals were given I^{131} . Therapy was, as anticipated, only moderately successful in spite of attempts to enhance the uptake of isotope by the preliminary use of thyrotropin and propylthiouracil. In one patient thyroidectomy fifteen weeks after the second dose of I^{131} provided tissue of some interest. Many nodules showed interstitial scarring similar to that seen in Figure 9 whereas others showed no change which might be ascribed to prior radioiodine therapy. Aside from the possible risk of covert malignancy it is apparent that such therapy accomplishes little in the management of non-toxic nodular goiters.

VII. Malignant Adenoma. Two patients with malignant adenoma were treated. Both had recurrence of tumor in the neck

but generalized metastases could not be demonstrated in either. The course of both patients was quite similar and may be illustrated by the following summary:

Patient Bru., aged eighteen, had had a large nodular goiter removed six years previously. A diagnosis of malignant adenoma was made. Within two years nodules in the neck reappeared and these were removed; the changes microscopically were similar to those found after the first operation. At the time that radioiodine was administered there were three nodules in the neck which were from 1 to 2 cm. in diameter. With a tracer dose of radioiodine it was found that the uptake by the tissue was as good as in some patients with Graves' disease. (Fig. 2.) Following 5 mc. of radioiodine a moderate decrease in the size of the nodules occurred. Two months after the first treatment 8 mc. were administered. Within five months from the initial treatment the nodules had disappeared. The patient was in a state of euthyroidism at all times. The course of the second patient was similar; subsequent to the administration of 9 mc. of radioiodine the estimated 45 Gm. of tissue became impalpable.

COMMENT

The results that have been presented indicate that radioiodine can be used to produce a remission of thyrotoxicosis in essentially all cases. In 100 patients with this disease complete remissions have been produced and maintained for one month or longer in ninety-five. In each of the 100 patients treated the thyroid gland decreased in size. In most of the patients with diffuse hyperplasia the gland became essentially normal or subnormal in size.

Although the exact mechanism of "cure" in thyrotoxicosis (like its etiology) remains obscure, the question arises as to whether "cure" following radioiodine is on the same basis as that following thyroidectomy. Although there is a similar result in the two therapies in that the total number of cells is reduced, there is a possibility that additional antagonizing effects from radioiodine are attributable to sublethal actions on the cells and to secondary results from the fibrosis produced. However, experiences

with prolonged treatment with thiouracil suggest that a reduction in the total number of cells is not a necessity for a remission to persist after cessation of treatment. To serve as a working basis we use the hypothesis that the more "bombardment" individual thyroid cells receive from thyrotropin the more likely they are to become refractory to further stimulation; thus a remission of thyrotoxicosis would result when the thyroid cells develop an adequate amount of refractoriness. The fewer cells present, the more "bombardment" each receives. Eventually the cells, however, may lose some of their refractoriness. Other things being equal, the more cells which remain viable the greater is the likelihood of reappearance of thyrotoxicosis. This hypothesis could explain the remissions that occur following thyroidectomy, radioiodine or thiouracil, and would account for the greater incidence of relapses with the latter therapy.

The main problem in the use of radioiodine is the difficulty involved in the selection of the appropriate dose. Excessive amounts may produce myxedema but persistent myxedema was encountered in only three of our patients. Transient hypothyroidism has been not uncommon in our experience. So long as the hypothyroidism is only transient it does not constitute a significant handicap; indeed, such states seem to lend assurance to the persistency of the remission. Our experience has yielded the clinical impression that hypothyroidism is transient more frequently following radioiodotherapeusis than following thyroidectomy. If this observation is borne out by further experience, it might be postulated that with irradiation of the thyroid some of the acinar cells temporarily may have a decreased capacity to manufacture hormone, but may later regain their normal physiologic activity.

The patients who developed the full-blown picture of myxedema developed it more slowly (three to six months) than generally occurs following thyroidectomy. Some of the factors which may account for this difference in response are (1) with

thyroidectomy a significant amount of hormone is removed along with the goiter, (2) following radioiodine many of the cells may continue to function at least partially for several weeks, either because this interval is required to kill the cells with radioiodine or for the scar tissue to contract enough to interfere significantly with their blood supply, or because of both factors.

Radioiodine can cause enormous reduction in the size of goiters but it does so chiefly by decreasing the number of acinar cells and probably secondarily by reducing the vascularity. It does not reduce the quantity of fibrous tissue or calcium, and apparently does not cause much reduction in colloid cysts. Therefore, in large toxic nodular goiters it can produce a complete remission in the thyrotoxicity and it can reduce the size of the goiter, but a large amount of inert tissue may persist. For this reason it probably will not offer much advantage in the treatment of the great proportion of large, non-toxic multinodular goiters.

The proper selection of patients for therapy with radioiodine must await further observation of individuals who have been treated in this manner and of those who have been given one of the thiouracils alone; more satisfactory comparisons with other methods of therapy can then be made. Upon the basis of present data, many factors should be considered in the selection of therapy for any individual patient.⁴ Radioiodine is a very simple form of therapy to the patient but it must be used only by a selected group of specialists. Therefore, it is not available to very many people. This type of treatment is generally less expensive than is thyroidectomy and is associated with less economic strain and physical discomfort. It is particularly worth while in patients who have become sensitive to certain antithyroid compounds and to those in whom complications from thyroidectomy loom as a good possibility, for example, individuals with hemorrhagic tendencies, those with severe cardiovascular disturbances, those who have developed hypo-

parathyroidism or nerve paralysis after previous thyroidectomies. Relatively good results were obtained in the treatment of two patients with malignant adenomas. However, the results in patients with highly

malignant neoplasms leave much to be desired.⁵

The results in the three patients treated with I^{130} were excellent. Indeed, this isotope might be superior to I^{131} were it readily available. Its much shorter half-life causes it to exert its effect upon the thyroid and the other tissues within a much shorter interval. Thus, the other tissues are exposed to its damaging effects for shorter intervals. Whereas with the larger doses required the tissues get more exposure within a short interval, the sum total irradiation is less than with the I^{131} because a significant amount of the latter is fixed to protein, due to continued and more prolonged function, and can be demonstrated for many weeks. The use of tracer doses of radioiodine as an indicator of the quantity of isotope to use therapeutically is more applicable with I^{130} than with I^{131} because of the fewer oscillations in the rate of thyroid function.

Whether radioiodine in the doses used in this study will exhibit a significant carcinogenic effect and also its possible deleterious effects in other parts of the body remain to be determined.

SUMMARY

A total of 111 patients have been treated with radioiodine; 106 had thyrotoxicosis; three had non-toxic nodular goiter and two had malignant adenoma. Six of the thyrotoxic subjects received their treatment too recently for adequate consideration. In ninety-two of ninety-seven patients treated with I^{131} a remission was produced and has persisted. Most of these patients became euthyroid within six months, an average of approximately three months. A total of 222 doses of radioiodine were given to ninety-seven patients; an average of 2.2 doses per patient. Thirty-five required only one dose; fourteen were given more than three doses. In the group experiencing remissions within six months, approximately 225 μ c. per Gm. of thyroid tissue were administered. An average total of about 8 mc. was required for thyrotoxic patients with diffuse hyperplasia of the thyroid and

TABLE XII
COMPARISON OF THE CLINICALLY ESTIMATED WEIGHT OF
GOITERS WITH WEIGHT OF THYROIDS REMOVED BY
SUBTOTAL THYROIDECTOMY

Case No.	Weight of Thyroid (Gm.)	
	Estimated	Found
1	35	45
3	40	42
10	25	31
12	30	26
17	140	180
28*	40	29
36	40	39
43	35	32
52*	30	22
56*	30	28
57	50	44
58	60	50
60	40	34†
63	30	21
64	50	40
67	70	61
68	70	71
70*	35	23
73*	60	42
74	40	39
75	50	33
76*	50	71
83	80	90
84	60	63
85	35	25
87	70	60
91	60	66
101	50	43
103	30	24†
111*	60	60
114	40	32
119*	100	169
121*	120	140
124	15	12†
127	40	32
128	40	41
129*	40	49
134	70	73
139	30	23
140	50	44
146	35	35

* Adenomatous goiters.

† These values have been derived by multiplying the weight of one lobe by two since only hemithyroidectomies were performed.

those previously thyroidectomized; twenty-two individuals with toxic nodular goiter required larger total doses although somewhat smaller in proportion to the size of the thyroid gland.

The goiter was reduced in size in all instances. Indeed, in all except one of the patients with diffuse hyperplasia the gland decreased to an estimated 25 Gm. or less; the one exception was an individual who declined to return for completion of therapy. In most of the patients with diffuse hyperplasia the thyroid became reduced to essentially normal or subnormal size before remission resulted.

Three patients developed persistent myxedema. In sixteen others transient hypothyroidism resulted.

Three individuals with thyrotoxicosis were treated with I^{130} with excellent results. In two patients with malignant adenoma the cervical masses became impalpable. Three subjects with non-toxic nodular goiter experienced only slight reduction in the size of the goiters.

No significant untoward effects from the radioiodine were manifested by non-thyroid tissues. One individual was pregnant at the time of her therapy, one had acute glomerular nephritis, one had chronic pyelonephritis, three had had acute hepatitis and several had congestive heart failure.

An outline of our present plan of therapy and a discussion of many factors concerned with iodotherapy are given in the following paper.

Appendix. Since careful evaluation of the size of the thyroid is of importance in determining the dosage of radioiodine required, it is important to know how accurately this may be determined. There was no opportunity to weigh the gland of the patients

before treatment with radioiodine. However, information obtained with other studies is of aid.

Several years ago one of us (R. H. W.) estimated the size of the thyroid of patients treated with thiouracil, and following subtotal thyroidectomy the gland was trimmed and weighed carefully as part of a procedure for determining the localization of thiouracil. The estimated and the determined weights of these glands are recorded in Table XII.

In interpreting the data it is to be borne in mind that the "determined weight" is not an exact indicator of the size of the gland as it exists in the patient because of variations in the amount of fluid lost or gained during the operation. Moreover, there were variations in the quantity of thyroid tissue left in the neck.

It may be observed that the error was greater in estimating the weight of adenomatous goiters than diffusely hyperplastic ones. In only three of thirty-one of the latter type was there a discrepancy of more than 10 Gm.

REFERENCES

1. HERTZ, S. and ROBERTS, A. The use of radioactive iodine therapy in hyperthyroidism. *J. A. M. A.*, 131: 81, 1946.
2. CHAPMAN, E. M. and EVANS, R. D. Treatment of hyperthyroidism with radioactive iodine. *J. A. M. A.*, 136: 86, 1946.
3. WILLIAMS, R. H., JAFFE, H., TOWERY, B. T., ROGERS, W. F. and TAGNON, R. Factors influencing the effectiveness of radioiodotherapy. *Am. J. Med.*, 7: 718, 1949.
4. WILLIAMS, R. H. Selection of therapy for individual patients with thyrotoxicosis. *J. A. M. A.*, 139: 1064, 1949.
5. RAWSON, R. W. and MCARTHUR, J. W. Radioiodine: its use as a tool in the study of thyroid physiology. *J. Clin. Endocrinol.*, 7: 235, 1947.
6. WILLIAMS, R. H., JAFFE, H. and KEMP, C. Effect of severe stress upon thyroid function. (In press.)

Factors Influencing the Effectiveness of Radioiodotherapy*

ROBERT H. WILLIAMS, M.D., HERBERT JAFFE, Ph.D., BEVERLY T. TOWERY, M.D.,†
Seattle, Washington New York, New York Nashville, Tennessee

WALTER F. ROGERS, JR., M.D. and RENE TAGNON, M.D.
Syracuse, New York Boston, Massachusetts

RESULTS presented in the preceding paper¹ as well as in the reports of other investigators^{2,3} demonstrate that in treating thyrotoxicosis with radioiodine some of the problems encountered are similar to those found with surgical



FIG. 1. Note the variations in the concentration of radioiodine in the thyroid.

therapy. The effectiveness of radioiodine, like subtotal thyroidectomy, depends upon the elimination of the majority of the thyroid acinar cells. Since only slight differences in the quantity and quality of tissue remaining may determine whether the amount of thyroid hormone produced is excessive, adequate or inadequate, it is imperative that this problem be evaluated carefully. An advantage is afforded surgical therapy by the opportunity of directly examining the gland, thereby aiding in determining how

much tissue should be removed; the operator can proceed immediately in extirpating whatever amount he chooses. More difficulty is encountered in selecting the optimal dose of radioiodine. The concentration of and duration of fixation of isotope in or adjacent to thyroid cells⁴ (Fig. 1) is a complex kinetic process which can be predicted only within certain broad limits. Even tracer-dose techniques do not reflect the alterations in iodine metabolism that occur during the weeks that I^{131} exerts its activity. The efficacy of radioiodine in reducing the amount of hyperplastic tissue is subject to influences which relate to net iodine-thyroid-pituitary interrelationships which in turn affect the ionizing radiation to which the thyroid is subjected over a considerable period of time. In this respect, the ingestion of goitrogens, variation in iodine intake, metabolic rate, stress,⁵ et cetera, should be mentioned.

In spite of certain difficulties inherent in the selection of dosage it is believed that radioiodine therapy is unquestionably the treatment of choice in certain patients and that its use is worthy of consideration in many others. Certain observations concerning the selection of doses of radioiodine in the treatment of 111 individuals with thyrotoxicosis are to be described.

METHODS

All of the radioiodine used in these studies was I^{131} . The quantities administered were based

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass., and from the Department of Medicine, University of Washington, Seattle, Wash.

† Research Fellow aided by the Commonwealth Fund.

upon estimates made at Oak Ridge, Tennessee, with standard corrections for decay. All of the therapeutic doses were administered by mouth and consisted of 1 mc. per 10 cc. of water. In most of the treatments approximately 0.5 mg. of potassium iodide was used as a carrier. None of the subjects received potassium iodide within four weeks of the test doses except where otherwise mentioned. The tracer dose consisted of 100 microcuries in 1 cc. of physiologic saline solution without added carrier; it was injected subcutaneously.

For the determination of the radioiodine in serum 0.5 or 1 cc. was placed in a bottle cap with one drop of dupanol. After drying in an oven the cap was placed under a Geiger-Mueller tube and counts were made. Urine was assayed in a similar manner.

For the determination of PBI* 1 cc. of serum was pipetted into a 15 cc. centrifuge tube. Then 9 cc. of 10 per cent trichloroacetic acid was added while the solution was stirred vigorously. After centrifugation the supernatant fluid was decanted. The precipitate was washed three times with 5 cc. portions of 10 per cent trichloroacetic acid, transferred quantitatively to bottle caps, dried at 100°C. and then isotope counts were made.

Estimates of the size of the thyroid gland were made in all instances by the same physician and were recorded in Gm. It is believed that these estimations were relatively close, especially when the gland weighed less than approximately 70 Gm.¹

The patients previously treated by means of thyroidectomy and those with nodular goiters are considered separately from those with diffuse goiter.

Fifty-six patients had received one of the thiouracils for prolonged intervals, as indicated in the figures. The dosage was sufficient to maintain the metabolic rate at a normal level.

RESULTS

Epithyroid Counts. Determinations of the concentration of isotope in the region of the thyroid gland were made in ten patients (Fig. 2) by placing a Geiger-Mueller counting tube successively over each lateral lobe of the gland. The counts were made twenty-four hours after therapeutic doses had been given. The counting tube was held 1 cm. from the skin and a leaded rubber pad was

placed between the neck and the counter. In a few instances similar counts were made over the region of the kidneys.

The amount of radioiodine found in the thyroid region could not be correlated well with the ultimate total dose required to

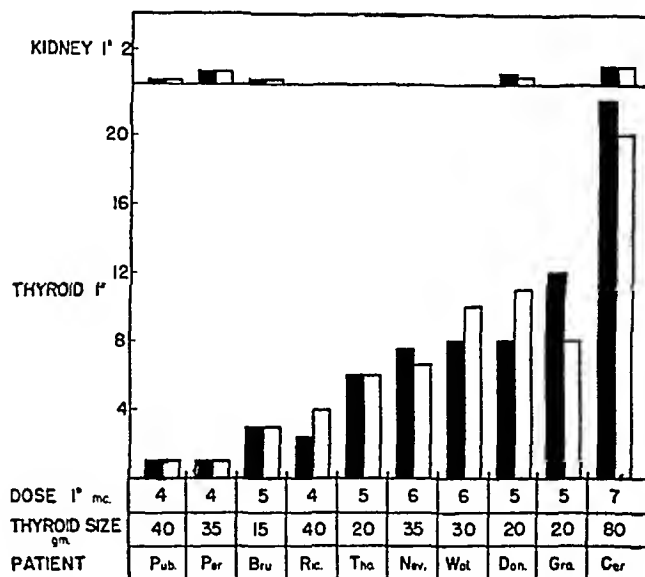


FIG. 2. In order to make allowance for the differences in the size of the thyroid gland in the correlation of the counts over the gland with the size of the dosage, the counts per second were divided by the dose in microcuries per 100 gm. of thyroid tissue. The same relative estimations were made with counts determined over the kidneys.

produce a sustained remission. The counts over each lateral lobe were quite similar. The counts over the renal regions were much less than over the thyroid. In one patient with severe acute glomerular nephritis (Per., Fig. 2) the concentration of isotope in the renal region was similar to that found in patients without kidney disease.

Relation of Radioiodotherapeusis to the Content of Radioiodine in Blood and Urine. 1. *Changes within One Hour after Tracer Dose:* Nineteen thyrotoxic patients received tracer doses of I^{131} . The subjects remained at rest for one hour and at this time determinations were made of the total amount of radioiodine which had been excreted and of its concentration in serum. A similar test was conducted in four athyreotic subjects and in seven normal individuals. The results are presented in Figure 3.

Considerable variation in the quantity of radioiodine in the serum and urine was

* Protein-bound radioiodine.

observed in the same as well as in different groups of subjects. Neither the content of isotope in the urine nor blood following the test dose was a satisfactory indicator of the quantity required to produce sustained re-

mission. There was no significant difference between those who experienced a remission and those who did not.

Most of the thyrotoxic subjects who experienced a remission in six months received an average of from 60 to 90 μ c. per Gm. of thyroid tissue per month, or a total of from 175 to 300 μ c. per Gm. Those who remained thyrotoxic received comparable amounts.

2. *Daily Excretion of Radioiodine in Urine Following Therapeutic or Tracer Doses:* Determination of the quantity of radioiodine excreted during the first twenty-four hours following therapeutic doses showed (Fig. 4) in most instances that from 20 to 40 per cent of the dose was excreted. Comparison of these values with the quantities of isotope used in producing remission within six months revealed no definite correlation whether the dosage was expressed as total millicuries, total microcuries per Gm. of thyroid, or the average number of microcuries per Gm. of thyroid per month. Furthermore, in these cases there was no significant effect on the quantity of radioiodine in the urine when standard treatment with propylthiouracil was continued until two days before isotope therapy.

In the group of patients followed for several days (Fig. 5) the quantity of radioiodine in the urine decreased considerably after the first one or two days following therapy, when as much as 1 per cent of the initial dose continued to be excreted daily for many days. The quantity of isotope in the urine of one patient (Ch.) given three therapeutic doses showed relative increases, while in another subject (Bo.) there was less after the second treatment than after the first. One individual (Si.) given two equal-sized tracer doses within three weeks, without any therapy in the interim, excreted 18 per cent within twenty-four hours after the first dose and 13 per cent after the second dose. By the end of the fourth day the total excretion was the same in each instance. The subject who took propylthiouracil until the day of radioiodine administration excreted relatively the same amount of isotope as did the patients who had not

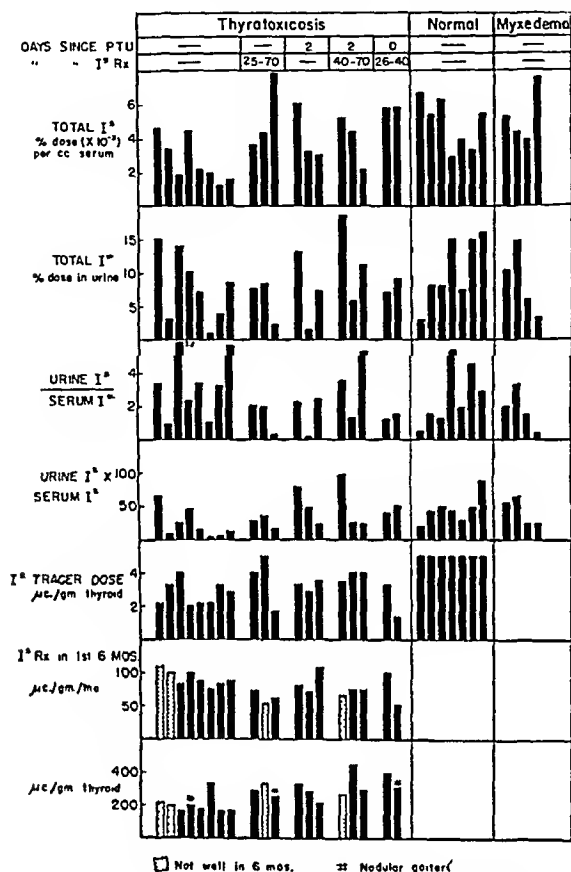


FIG. 3. Each column presents data in a different patient. All of the subjects experienced a remission within six months after the initial radioiodine treatment, except where indicated. The myxedema patients had been treated with desiccated thyroid for several months before the tests with radioiodine were conducted; their metabolic rates were within normal limits. The patients treated with propylthiouracil (PTU) had received from 200 to 250 mg. daily, ending at the times indicated. The thyrotoxic subjects previously treated with radioiodine had received therapeutic doses. Although some isotope was still present in these patients, the quantities were relatively insignificant. Tracer doses (100 mc.) were given each subject. The ratio of the total amount of isotope in the urine to its concentration in 1 cc. of plasma and the product of these values have been plotted since in other studies⁶ these calculations have accentuated the differences between thyrotoxic, normal and myxedematous individuals. The clinical response during the first six months only is considered here because most of the subjects experienced a remission during this interval and because treatment beyond it was given more irregularly and was more complicated by repair processes in the thyroid gland.

received this therapy. On the other hand, the subject taking potassium iodide excreted relatively more.

The quantity of radioiodine that was excreted during the intervals studied was a poor index of the total dose required to

produce a remission. The patients who had diffuse goiters became euthyroid after receiving from 70 to 90 $\mu\text{c.}$ per Gm. of thyroid per month; those with nodular goiters needed less per Gm. of tissue but a greater total quantity.

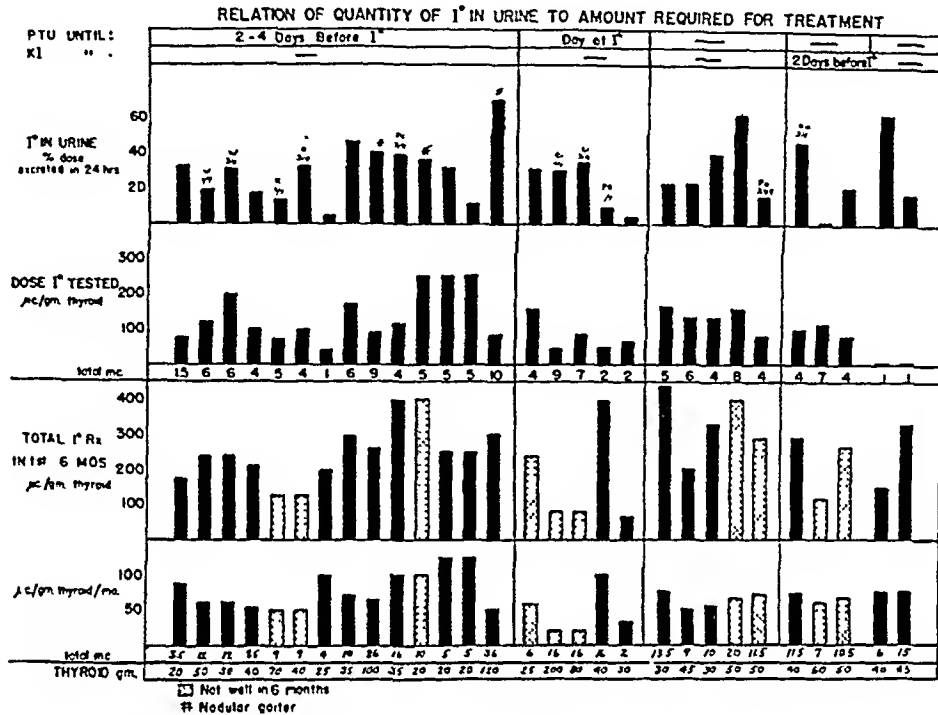


FIG. 4. See legend for Figure 3. In some patients, as indicated on the chart, the same test was conducted twice. For comparative purposes the patient's initial and the date of the test are included in the data. The weights of the thyroid are those estimated at the time of the first radioiodine treatment.

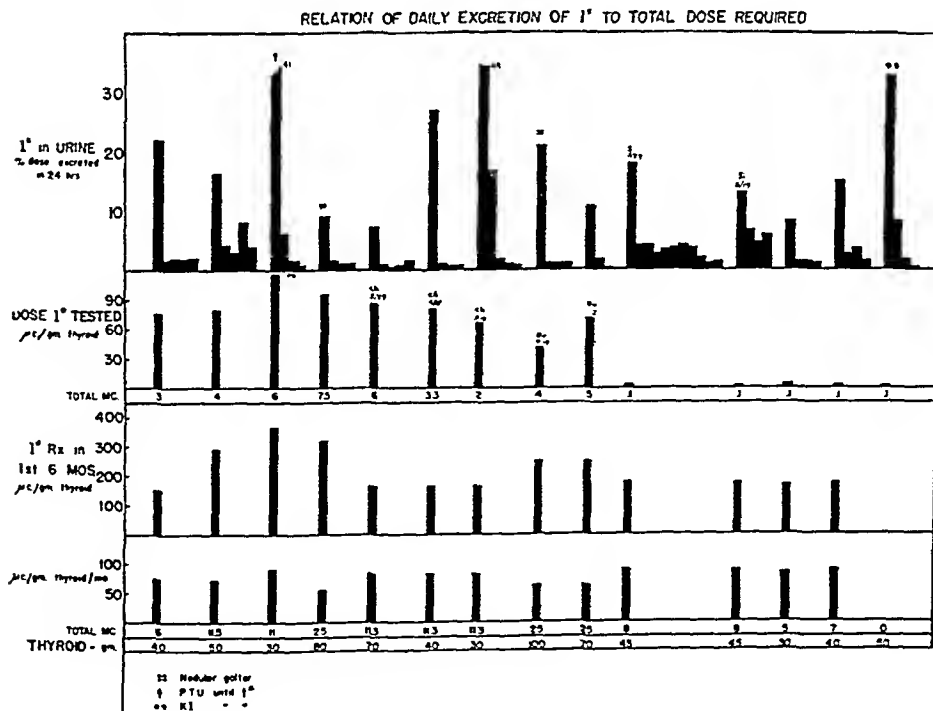


FIG. 5. See legends for Figures 3 and 4. Each of the patients included in this figure experienced a remission within six months and it has been sustained subsequently.

Relationship of the Physical Characteristics of the Thyroid Gland and the Intervals of Therapy to the Dosage Used to Produce Remission. There is no way of determining the minimal dosage required to produce a remission in a given patient but experience permits reasonable estimates. The results in patients with

rate. However, in some subjects with toxic diffuse goiter apparently a difference of 1 or 2 mc. in dosage will determine whether hyperthyroidism or euthyroidism will be produced; in other instances this same difference in dosage may determine whether euthyroidism or myxedema will develop.

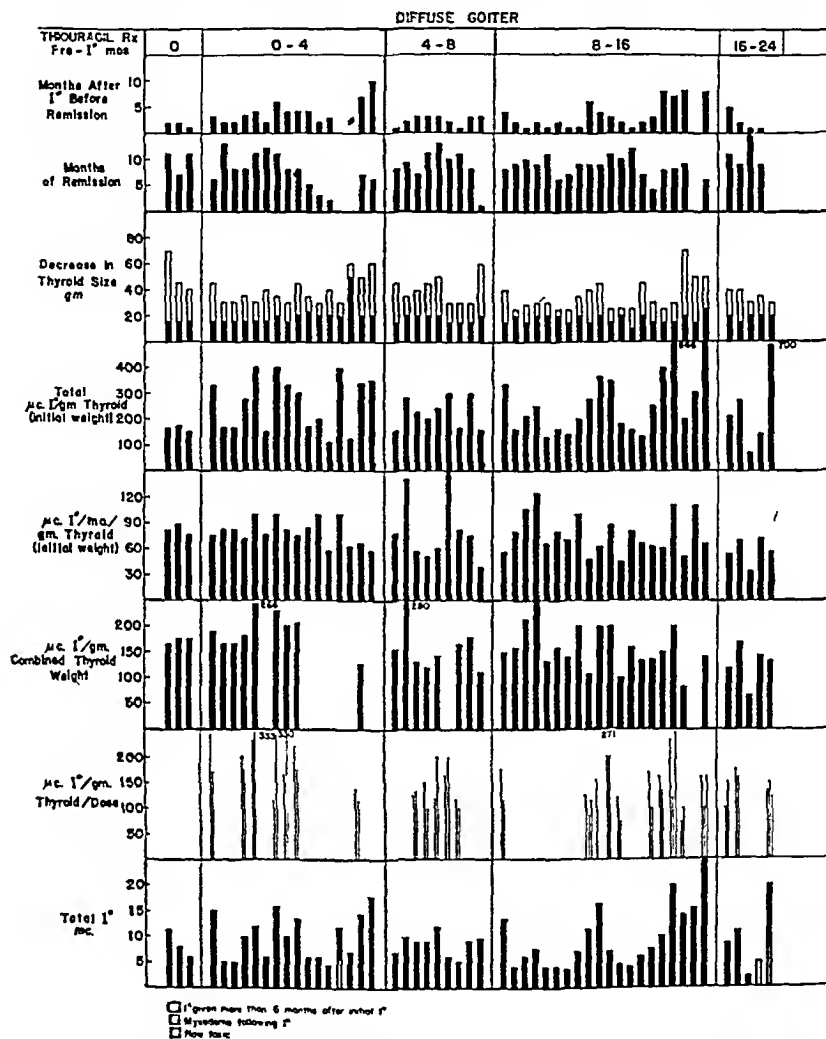


FIG. 6. Each column indicates data in one patient. In the top row is demonstrated the interval from the first dose of radioiodine until a remission was obtained that has been sustained. The present size of the thyroid glands is demonstrated by the black columns, while the blank portions of the columns show the extent to which they have decreased in size. The method and rationale of calculation of the $\mu\text{cI}^*/\text{mo./gm.}$ thyroid and the $\mu\text{cI}^*/\text{gm.}$ combined thyroid weight (or average thyroid weight) have been presented in the text. In the section labeled $\mu\text{cI}^*/\text{gm.}$ thyroid/dose are presented the data in patients given more than one radioiodine treatment within the first six months of therapy. One patient, indicated by #, did not return for additional therapy.

toxic nodular goiters indicate that in some instances, even after a state of euthyroidism is established, 10 mc. or more of radioiodine may be given without altering the metabolic

In Figure 6 are presented some of the results obtained in patients with toxic diffuse goiter. Because many patients had been treated with one of the thiouracils for

varying intervals and inasmuch as sustained remissions may follow such therapy, the cases are separated according to the intervals of previous treatment with these compounds. (Fig. 6.) In each patient it was clearly established that the individual was

propylthiouracil was given immediately before the radioiodine but usually was stopped about four days before the latter.

It may be observed (Fig. 6) that all but two of the patients with diffuse goiters experienced remission of thyrotoxicosis.

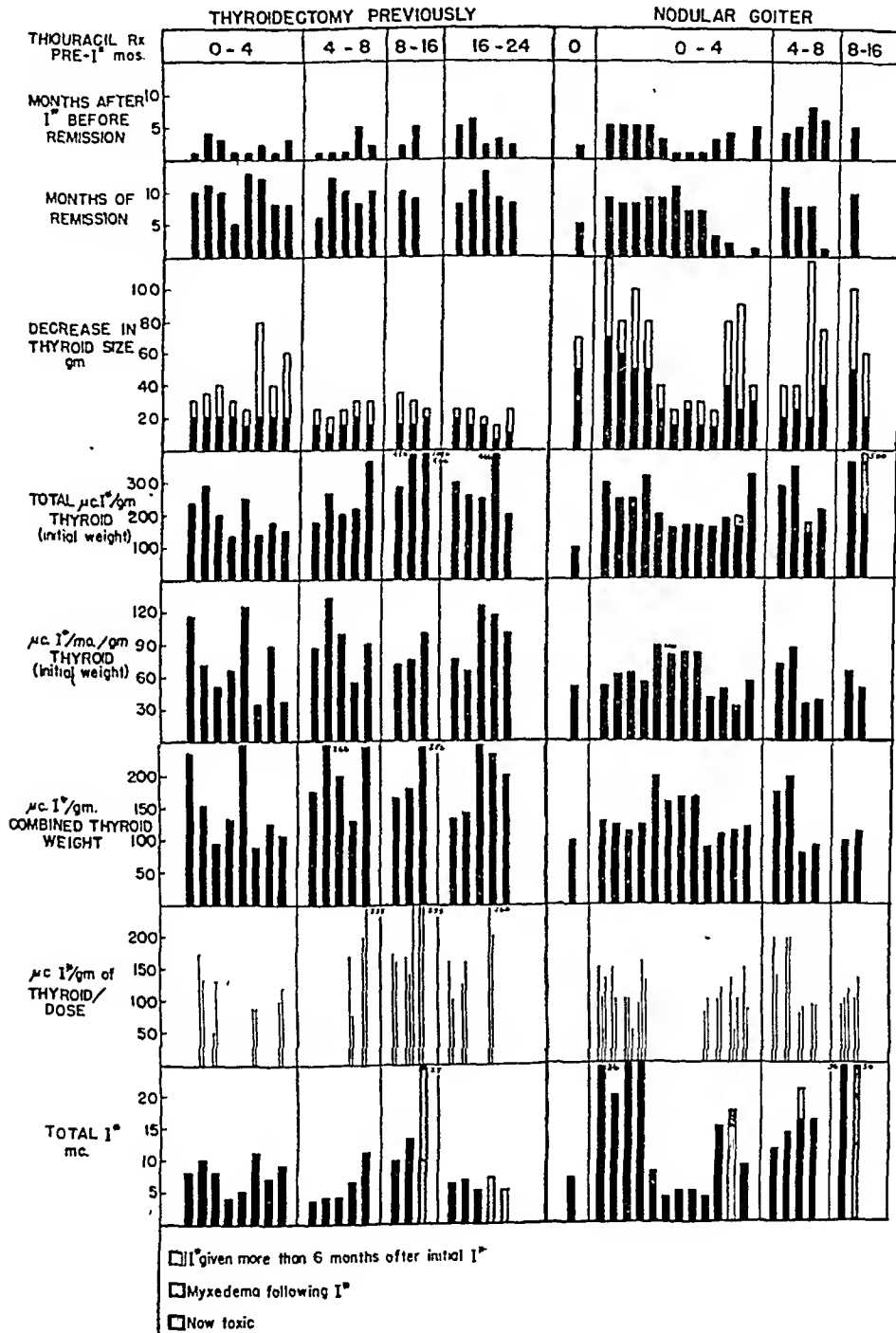


FIG. 7. Compare with Figure 6.

thyrotoxic when this therapy was withdrawn. Thus the radioiodine was not given immediately after long intervals of thiouracil treatment but was separated from it by one or more months. In some of these cases a short course, one to five weeks, of

Moreover, in all but seven cases the remission occurred within six months. One subject developed myxedema. The thyroid in all patients decreased to 25 Gm. or less except in one who failed to return after the initial dose of radioiodine.

There is no statistically significant difference in the dosage of radioiodine used to produce remission in the groups of patients previously treated for varying intervals with thiouracil.¹ The patient (Fig. 6) who developed myxedema following radioiodine

Moreover, many of the nodular glands remained enlarged although remissions of the thyrotoxicosis developed. Two patients with nodular goiter have remained thyrotoxic in spite of 17.5 mc. in one case and 30 mc. in another. Two individuals who

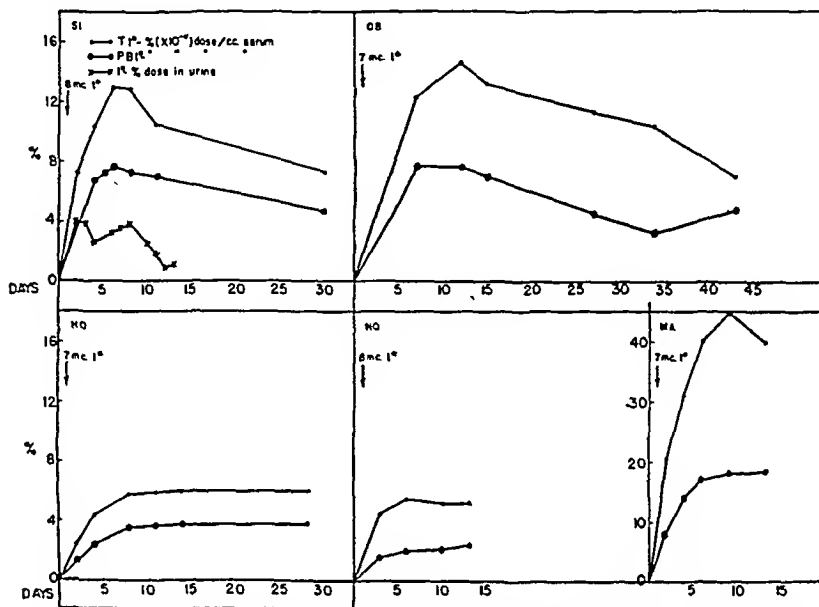


FIG. 8. The plots in the upper half of the figure are in patients with diffusely enlarged thyroids but the others were nodular. No. and Ma. had no thyrotoxicosis but the others were severely toxic. Each patient received 0.3 mg. KI with the radioiodine, but none received KI or PTU following it. No. received 50 J.S. units of thyrotropin in sesame oil for each of two days before I¹³¹. All of the thyrotoxic patients have had remissions which have now lasted for more than seven months. The diffusely enlarged glands decreased in weight from approximately 45 gm. to less than normal size (20 gm.); the nodular glands decreased only slightly. Following removal of Ma.'s gland several months later characteristics of a thyroid storm were observed, although repeated clinical examinations, including estimations of the basal metabolic rate, had shown no evidence of thyrotoxicosis.

had had prolonged therapy with thiouracil; without thiouracil thyrotoxicosis reappeared, although of much milder degree. He received less radioiodine than the average quantity given to other patients. On the other hand, another individual who had taken thiouracil for more than two years and whose thyroid gland weighed approximately 30 Gm. has continued to have thyrotoxicosis after 20 mc.

Upon comparing Figures 6 and 7 it may be observed that there was no significant difference in the dosage used in the different groups when expressed upon a thyroid-weight basis. The total amount used in the subjects with toxic nodular goiters was greater than in those with diffuse goiter.

had had a thyroidectomy and had been treated with thiouracil for intervals of from sixteen to twenty-four months developed myxedema. Neither received as much as the average amount given to the other patients.

Change in the Total and Protein-Bound Radioiodine Content of the Serum Following Therapeutic Doses. Aside from the usual factors which affect iodine metabolism, further changes are produced by radioactivity. As a result of the latter action a decreased rate of synthesis of PBI* and a relative increase in "spillage" of PBI* and PBI from the thyroid gland may be anticipated. The extent to which this "spillage" phenomenon takes place, with the increased metabolic rate which it may produce, may be expected to

effect the quantity of TI^* and PBI^* in the body.

Following the administration of therapeutic doses of radioiodine the changes in PBI^* were determined in sixteen patients and the TI^* in eleven for intervals of from

thyroid cells,⁷ the resulting injurious effects on the cells would probably decrease the synthesis of PBI^* . On the other hand, the injured tissue might permit a greater "spillage" into the blood stream of such PBI^* as had been synthesized. As a final

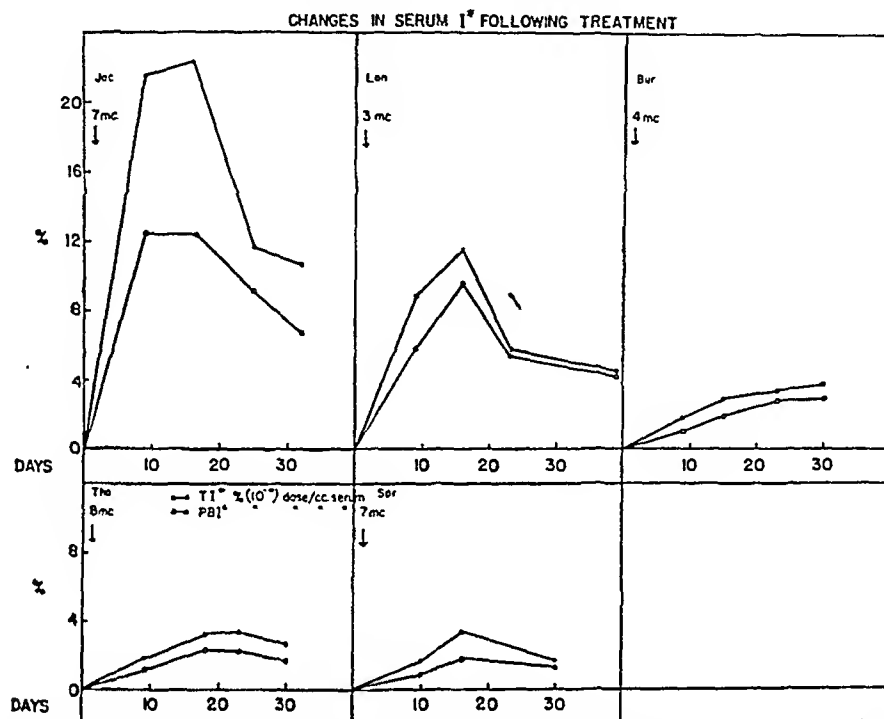


FIG. 9. Each of these patients had thyrotoxicosis; it was severe in Jac. and Tho. The thyroid was diffusely enlarged in Jac. and Lon. and was nodular in the others. Approximately 30 gm. of tissue were estimated to be present in Lon. and Bur. and 75 gm. in the others. The treatment of these patients was especially different from that of the patients in Figure 8 in that twelve hours after the radioiodine was administered each patient was given 3 drops of a saturated solution of potassium iodide and he continued to receive it twice daily for five days; it was then discontinued. Bur. and Spr. experienced remissions in thyrotoxicosis that have persisted for more than six months, but additional PBI^* was given to the others within six weeks.

two to six weeks. Fourteen of the patients had thyrotoxicosis; five of the fourteen had nodular goiters. Two individuals had non-toxic nodular goiters.

The serum values and some of the characteristics of each case are given in Figures 8, 9 and 10. The subjects charted in Figure 9 were given potassium iodide for five days following radioiodine while those in Figure 8 were not. The increased quantity of iodine in the body would promote more rapid excretion of radioiodine. Since iodine tends to inactivate thyrotropin, one would anticipate that this therapy would cause a slower synthesis of PBI^* but an increased tendency for its storage in the thyroid. Because iodine promotes a longer stay of radioiodine in the

result of these effects of iodide a slower increase in the serum of TI^* and PBI^* might be anticipated with less of a total increase. However, a decreased rate of utilization of PBI^* probably results as the metabolic rate decreases.

The maximal concentrations of PBI^* were found between the fifth and twentieth days. During this interval there also tended to be the greatest difference between the concentration of TI^* and PBI^* . In each patient significant concentrations were found for as long as the patients were followed, which in one instance was six weeks. In no instance did the PBI^* ever account for all of the TI^* although these two values tended to approach each other after the

twentieth day. The TI^* and the PBI^* reached higher levels in the patients with diffuse goiter than in those with toxic nodular glands. In the latter group the rise in TI^* and PBI^* was slower; there was a more prolonged plateau, a slower fall and less of a difference in the TI^* and PBI^* .

by the isotope can be readily determined but its effectiveness in controlling thyrotoxicosis is dependent upon a large number of factors which modify its concentration and distribution in the thyroid. Apparently the metabolism of radioiodine is like that of iodine. Some of the factors influencing

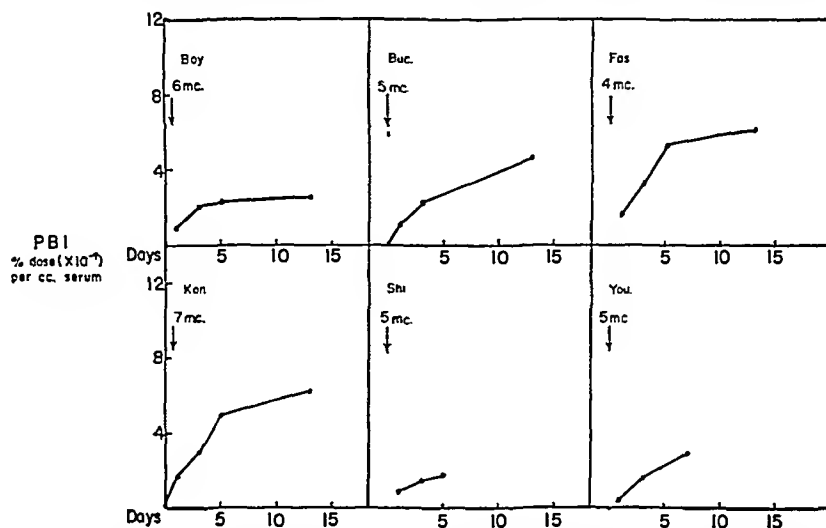


FIG. 10. Boy. had a nodular goiter with severe thyrotoxicosis; in the others the disease was less severe and the gland was diffusely enlarged. Potassium iodide therapy was like that given the patients described in Figure 8. The thyroid gland of Buc., Fas., Shi. and Kon. weighed approximately 30 gm. and decreased to less than 20 gm. within several weeks following radioiodine therapy. In Boy. the gland weighed 60 gm. before and after the therapy shown. Buc. developed myxedema; Fas., Shi. and You. have needed no more therapy; after 3 mc. of additional treatment Kon. experienced a remission.

The concentration in patient Ma. Fig. (8) became much greater than in any of the others. This subject had a nodular goiter which clinically was non-toxic but microscopically it appeared very active. This patient is unique in several respects and is being investigated further.

The nature of the plots in Figures 8, 9 and 10 does not indicate the efficacy of the therapy with reference either to the reduction in gland size or thyrotoxicity.

COMMENT

The effectiveness of radioiodine in the treatment of thyrotoxicosis is due to its capacity of 'injuring' thyroid acinar cells, leading to disappearance of a large proportion of them. Its efficiency depends upon the amount and duration of exposure of the individual thyroid cells to ionizing radiation. The amount of radioactivity possessed

the distribution of the latter are discussed below.

Thyrotropin causes (1) an increase in the rate of transfer of thyroid hormone from the thyroid acini to serum, (2) a decrease in the storage of hormone in the thyroid gland, (3) hypertrophy and hyperplasia of the acinar cells, (4) an increase in the rate of transfer of iodide from the serum to the thyroid, (5) an increase in the rate of synthesis of the thyroid hormone and (6) an increase in the rate of transfer of iodine from the cells to the lumen of the acinus. The quantity of thyrotropin released is influenced, presumably, by many factors such as the quantity of iodine in the diet and amount of stress. Moreover, factors which affect its inactivation and excretion would also influence, indirectly, the exchange of iodine in the thyroid.

Iodine inactivates thyrotropin and tends

to inhibit its effects. Moreover, the quantity of iodine in the body may exert significant effects upon the exchange of radioiodine in the thyroid independent of its effects on the thyroid, for example, upon the serum; thyroid iodine gradient, excretion of iodine in the urine, etc. Among the factors affecting the quantity of iodine in the body are the amount ingested in food or as medicine and the quantity in water and in air. The quantity of iodine in the thyroid is influenced by the amount in the blood; anti-thyroid substances in the diet, thioureas, thiocyanates, etc.; thyrotropin activity and the structure of the thyroid. Of course, many of these effects are interdependent.

Results and Present Plan of Therapy. Some of the variables influencing response can be assessed following the administration of radioiodine by the determination of (1) the concentration of isotope in the thyroid region, (2) its excretion in the urine, (3) its concentration in the blood and (4) correlation of these observations with gland size and time. However, many factors must be considered in interpreting the data obtained. For example, following a tracer dose the concentration in the thyroid region can be used as an indication of the relative quantity of therapeutic dose of isotope which will accumulate in the same region when given under the same conditions. Likewise, by estimating the quantity of radioiodine in the blood and urine, it can be adduced that a significant portion of the remainder is in the thyroid gland.^{8,9,10} However, such information does not indicate the variations in concentration which may occur from cell to cell nor indicate the variations in ratios of concentration in cells and colloid. Furthermore, it must be emphasized (1) that I^{131} continues to irradiate the gland for several weeks and (2) during this interval the radioiodine is passing in and out of the gland repeatedly. In this connection it should be noted that as the injury of the acinar cells occurs, changes probably occur to alter the exchange of iodine in the thyroid and, therefore, make it different from the changes indicated in the beginning by

the tracer studies. Moreover, it seems likely that all thyroid acinar cells do not have the same degree of radiosensitivity and, consequently, the concentration of isotope in the cell is not an exact indicator of the extent of injury that will result in it.

In spite of the many variables which may interfere with accurate estimation of the dosage of radioiodine needed we are very much in favor of extending the types of tests that have already been applied, as well as searching for new tests, because determination of the dosage needed is by far the most important phase of radioiodotherapeusis. Perhaps more helpful information can be obtained by following the changes in the distribution of radioiodine for several weeks following its administration.

The regimen that was used most commonly in the treatment of our patients consists of (1) discontinuation of iodide therapy at least four weeks before radioiodine is to be given, (2) administration of propylthiouracil for approximately four weeks, ending four days before the administration of radioiodine, (3) the use of 0.5 mg. of potassium iodide twice daily, beginning within twelve to twenty-four hours after radioiodine and continuing for five days, (4) the administration of another dose of isotope approximately eight weeks later, if indicated. Of course, it is difficult to know the value of some of these measures but some reasons for their plausibility may be discussed.

Early in our experience¹ a few patients developed a distinct exacerbation in their condition within a few days following radioiodotherapeusis. These were individuals who had no previous therapy of any type for thyrotoxicosis. It was reasoned that radioiodine had altered thyroid physiology in a manner similar to thyroidectomy, except that there was not the degree of alarm reaction associated with the latter. After thyroidectomy thyroglobulin can be found in the blood almost immediately thereafter and thyroid storm is most apt to occur in the first twenty-four hours. Although estimations of thyroglobulin following radio-

iodine have not been reported, it seems very probable that with the necrosis of the thyroid tissue resulting from irradiation thyroglobulin could enter the blood stream just as it has been shown¹¹ to do in patients with thyroiditis. An appreciable amount of necrosis would not be expected for several days and the maximal intensity of the exacerbation in thyrotoxicity requires a similar interval. Apparently, with radioiodine or by surgery, the release of significant amounts of thyroid hormone into the blood stream of a patient who already has a relatively high concentration and is in poor general nutritional state may lead to a thyroid storm. On the other hand, when such patients are treated adequately for several weeks with propylthiouracil, a decreased concentration of hormone results in the thyroid and other portions of the body together with an improved nutritional status; therefore, they are less subject to untoward reactions. In some instances propylthiouracil is given for intervals longer than four weeks and sometimes less, depending upon the severity of the thyrotoxicosis, the interval before the next expected shipment of radioiodine, etc. Propylthiouracil not only has this advantage but it promotes improvement in the patient while waiting for the isotope. Moreover, it probably increases the uptake of the radioiodine by the thyroid if discontinued four days before the latter. Essentially all of the drug disappears from the body during this interval. If it is given until the day of the iodotherapy, it may interfere with the uptake of iodine by the thyroid.

The extent to which propylthiouracil interferes is small compared to the effects of therapeutic doses of potassium iodide. Although this substance probably does not cause significant interference for as long as four weeks after cessation of its administration, there are enough variables of other types to make it desirable to remove any that are not necessary. The use of propylthiouracil preceding radioiodine therapy helps eliminate excesses of iodine in the body. Whereas statistically significant differ-

ences were not found, we have the impression based upon careful consideration of individual cases that patients previously treated for long intervals with thiouracil, or previously subjected to thyroidectomy or both, require relatively less radioiodine than patients not so treated.

Young patients were not given as large doses initially as adults, as we particularly desired to avoid myxedema in this group. We attempted to select the minimal dose which we thought might produce a remission, realizing that it was easier to give additional doses than to treat myxedema. A rule-of-thumb* which evolved for application in the selection of the initial dosage for a great proportion of patients with diffuse hyperplasia was as follows: 4 mc. if the gland weighed 30 Gm., and 1.5 mc. extra for each additional 10 Gm. in weight. Of course, as discussed at length, there are many factors modifying the dosage required.

The use of the carrier doses of iodide was based upon the work of earlier investigations.² On the basis of our clinical studies we could not detect a definite difference in response whether we gave potassium iodide, sodium bromide or nothing with the radioiodide. It was difficult to evaluate the influence of potassium iodide upon the effectiveness of radioiodine when given for five days after the latter. Whereas such a procedure tends to promote excretion of radioiodine and from this point of view would decrease its effectiveness, potassium iodide helps trap the isotope in the thyroid cells⁷ which is where it is most desired. Whether or not this phenomenon is actually advantageous, iodide for a few days does help prevent exacerbations of the thyrotoxicity. Moreover, using it in the manner described apparently does not interfere significantly with interpretation of the effectiveness of radioiodine or in the next treatment with it.

The problem of when to give additional doses of radioiodine ranked next in difficulty

* This "rule-of-thumb," like so many others, probably will not hold very long but when applied to a limited group of patients it may be of aid for a while.

to the selection of dosage. In our earlier experiences we sometimes erred by repeating the treatment within four or five weeks. Now, with only few exceptions, we do not repeat the therapy within intervals less than approximately eight weeks. The interval required for patients to obtain a maximal response from a dose of radioiodine varies from one to five months. In general, patients who had had no definite response in six weeks or those who had had the maximal improvement after about four weeks and were experiencing an intensification of the manifestations by the sixth week invariably needed more therapy. The patients who were very mildly toxic by the end of eight weeks were followed for another two to four weeks before decision regarding additional therapy was made. Most of the patients who did not require additional therapy became euthyroid or hypothyroid within five to ten weeks. Patients who became myxedematous required three months or more to develop this picture. A few patients required three or four months to exhibit the maximal response to a given treatment although they did not develop myxedema. To illustrate the relative interval required for different degrees of response, the following "rule-of-thumb" may be stated: the maximal response in metabolic rate occurs within one month when treatment is inadequate, within two months when it is adequate and within three months when it is excessive. Of course there are notable exceptions to these generalizations.

The interval between the time of administration of radioiodine and remission of thyrotoxicosis is required not only to produce injurious effects on the thyroid cells but also to utilize the excess of hormone that had been manufactured previously. Since there is considerable variation in these respects, it is not surprising that the degree of response differs. For example, these factors are probably major ones in accounting for the slower response in metabolic rate of patients with toxic nodular goiter than in those with toxic diffuse goiter, while it was more rapid in those previously

thyroidectomized. The greater variation in the physiologic and anatomic status of the thyroid of patients with nodular goiters than those with diffuse hyperplasia contributes to the greater irregularity in response. The fact that none of the former group developed hypothyroidism, although relatively large doses of radioiodine were given when the patients were euthyroid, can be attributed at least partially to the greater variation in the physiologic activity of the thyroid cells.

SUMMARY

In our experience with radioiodine in the treatment of 111 patients with thyrotoxicosis the quantity of isotope required to produce remission varied considerably.

In investigating technics that might be used as indicators of the amount of isotope needed, we attempted to correlate the dosage of isotope used with (1) earlier estimations of amounts of it in blood, urine or thyroid region after specific intervals and (2) clinical examination of the thyroid gland.

None of the methods was very satisfactory. Clinical evaluation of the thyroid gland was of moderate aid. Nodular goiters required larger total amounts of isotope than diffuse goiters but less per Gm. of thyroid. Previous therapy with thiouracils for long intervals or with thyroidectomy did show statistically significant differences in the quantity of radioiodine needed, except insofar as they affected the quantity of thyroid tissue present.

The value of the administration for short intervals of propylthiouracil before, and of potassium iodide after radioiodotherapeusis is discussed along with many other factors affecting the results of therapy.

REFERENCES

1. WILLIAMS, R. H., JAFFE, H., TOWERY, B. T., ROGERS, W. F. and TAGNON, R. Radioiodotherapeusis. *Am. J. Med.*, 7: 702, 1949.
2. HERTZ, S. and ROBERTS, A. The use of radioactive iodine therapy in hyperthyroidism. *J. A. M. A.*, 131: 81, 1946.
3. CHAPMAN, E. M. and EVANS, R. D. Treatment of

- hyperthyroidism with radioactive iodine. *J. A. M. A.*, 136: 86, 1946.
4. LEBLOND, C. P. Localization of newly administered iodine in the thyroid gland as indicated by radioiodine. *J. Anat.*, 77: 149, 1943.
 5. WILLIAMS, R. H., JAFFE, H. and KEMP, C. Effect of severe stress upon thyroid function. (To be published.)
 6. WILLIAMS, R. H., JAFFE, H. and BERNSTEIN, B. Comparisons of the distribution of radioactive iodine in serum and blood in different levels of thyroid function. (To be published.)
 7. LEBLOND, C. P. Presented before the Laurentian Hormone Conference, St. Adèle, Quebec, September, 1947.
 8. HAMILTON, J. G. and SOLEY, M. H. Studies in iodine metabolism by the use of a new radioactive isotope of iodine. *Am. J. Physiol.*, 127: 557, 1939.
 9. HAMILTON, J. G. and SOLEY, M. H. Studies in iodine metabolism of thyroid gland in situ by use of radioiodine in normal subjects and in patients with various types of goiters. *Am. J. Physiol.*, 131: 135, 1940.
 10. HERTZ, S., ROBERTS, A. and SALTER, W. T. Radioactive iodine as an indicator in thyroid physiology. *J. Clin. Investigation*, 21: 25, 1942.
 11. LERMAN, J. Iodine components of blood. Circulating thyroglobulin in normal persons and in persons with thyroid diseases. *J. Clin. Investigation*, 19: 555, 1940.

Radioactive Iodine, I-131, in the Treatment of Hyperthyroidism*

SIDNEY C. WERNER, M.D., EDITH H. QUIMBY, M.D. and CHARLOTTE SCHMIDT, M.D.

New York, New York

RADIOACTIVE iodine (I^{131} eight day half-life) is an agent for the treatment of toxic goiter which has been studied at the Presbyterian Hospital for the past three years. The present report summarizes our experience in 103 patients.

When this work was initiated, information concerning dosage was scant.^{1,2} Hence the first patients were treated more or less empirically. On the basis of known physical data and from previous experience with x-ray therapy it was calculated that a dose of 3 to 4 millicuries of I^{131} would deliver a satisfactory irradiation to a moderate sized thyroid. It was soon noted that failure to respond to this dosage occurred mostly in patients with initially large glands and in those markedly thyrotoxic.³ A second dose of 3 to 4 mc. was given to most of these patients four months after the initial treatment but with no better response.⁴ By January, 1948, the accumulated data indicated that about 50 to 100 μ c. I^{131} retained per estimated Gm. of thyroid tissue resulted in satisfactory remission in a high percentage of cases.⁵ Since the average retention of I^{131} after ingestion is about 50 per cent of the administered amount, the administration of approximately 100 to 200 μ c. per estimated Gm. of gland weight would approach the desired goal. A total dosage of about 3 to 15 mc. would thus be required. However, for fear of inducing a high incidence of hypothyroidism it was decided to limit the highest dosage to 6.5 mc. and to retain the lower limit at 3 mc. Larger glands accordingly received some-

what less than the desired amount of I^{131} per Gm. of gland tissue and smaller ones somewhat more. Those patients failing to show remission within four months on such dosage were retreated. A final third dose was given to the few patients who remained uncontrolled four months later.

Forty patients were treated prior to January, 1948, and sixty-three patients from then to February, 1949, with a follow-up period of from almost three years to a minimum of at least four months. The results obtained indicated considerable success in inducing remission of hyperthyroidism by means of radioiodine (I^{131}).

METHODS

The earlier methods of Hertz,¹ Hamilton and Soley² and others^{6,7} for radioiodine therapy in hyperthyroidism have been reported. The relative merits of I^{130} (twelve hour half-life) and I^{131} (eight day half-life) have been discussed.⁸ At the present time, with I^{131} readily available from the atomic pile at Oak Ridge, the shorter-lived isotope no longer is employed. I^{131} was made available by the Atomic Energy Commission for investigative use in September, 1946. Since then the material has been obtainable in relatively large quantities, at low cost and essentially carrier-free (that is, not mixed with stable iodine). This last specification is important since it insures against the production of unwanted biologic effects due to iodine *per se*, as opposed to the desired radiation effects resulting from the gradual breakdown of the radioiodine.

Adequate arrangements are necessary for the safe handling of isotopes to avoid radiation dangers. The establishment and maintenance

* From the Departments of Medicine and Radiology, Presbyterian Hospital and the College of Physicians and Surgeons, New York. This investigation was supported (in part) by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health. Aided (in part) by a grant from the Council of Pharmacy and Chemistry, American Medical Association.

of these precautions was made the responsibility of a health officer. There were a number of problems connected with the clinical use of radioiodine. These included handling the isotope prior to its administration to the patient and the subsequent proper disposal of the patient's excreta. The avoidance of irradiation of other individuals from the material in the patient had to be considered although this hazard is generally not incurred to a significant extent in the treatment of hyperthyroidism. These problems have been discussed in detail elsewhere.⁹

The subject of radioiodine standardization has been the source of considerable confusion. "Millicuries," as reported in the literature, may represent widely discrepant values.¹⁰ All clinics in New York City have for two years employed a "New York millicurie" (corresponding, fortunately, to the one already employed in this clinic). This unit is about 1.4 times as great as the millicurie used by Oak Ridge until July 1, 1949, and is within 10 per cent of the unit now in use there. All doses herein reported are in terms of the New York millicurie.

The desired amount of I^{131} for either tracer or therapeutic use is diluted in water for ingestion by the patient. The container is then carefully rinsed and the washings also swallowed to insure against loss of activity. The patient need not be in the fasting state unless the rate of accumulation of radioiodine in the thyroid¹¹ is being studied. Twenty-four hours after ingestion of the I^{131} the uptake by the thyroid is measured.¹² At this point uptake is usually maximal and tends to reach a plateau.

Per cent uptake is determined by direct measurement over the thyroid gland with the Geiger counter. Necessary precautions in making such measurements have been discussed in detail elsewhere.⁹ It is sufficient to point out here that the counter must be at a great enough distance and have a large enough aperture so that radiation from the entire gland is measured. Approximation of thyroid uptake from urinary excretion is definitely less satisfactory^{13,14} and has been used at the Presbyterian Hospital only to supplement uptake studies.

Knowledge of I^{131} uptake by the thyroid is important in calculating radiation delivered to the gland. The radiation delivered to the thyroid depends both on the amount of I^{131} deposited per Gm. of gland tissue and its rate of biologic elimination due to secretion as iodine-

containing hormone. The formula for calculating dosage is:

$$\begin{aligned} &\text{Equivalent roentgens (e.r.)} \\ &= \frac{\text{mc. administered} \times \% \text{ uptake}}{\text{gland weight}} \times \frac{\text{effective}}{\text{half life} \times 160}. \end{aligned}$$

The term "equivalent roentgen" has been devised to include both beta and gamma ray dosage since the "roentgen" properly applies only to X and gamma rays. For practical evaluation of dosage the roentgen and equivalent roentgen may be considered to be the same. The magnitude of the equivalent roentgen (e.r.) is essentially the same as that of the "rep" used by some workers.

The determination of gland weight as used in the dosage formula is admittedly the least accurate part of the calculation. Gland size can be only roughly approximated. The practice of this clinic has been to rely on the results of palpation carried out by the same individual (S. C. W.) in all cases. Subsequent comparison of these estimates with a series of plasticine models representative of varying sizes of the thyroid is then made as an aid in classification.³ Soley, after comparing his own estimates of gland size from palpation with those made from specimens obtained subsequently at operation, calculated a discrepancy of about 30 per cent between the two.¹⁵ This agrees with our own approximation of error involved.

The term "effective half life" in the dosage formula above is used to express the deviation from the physical half life of eight days which results from the gradual loss of radioiodine from the gland as hormone secretion. If this elimination or secretion did not occur, the isotope would remain in the gland for total decay, delivering its radiation at a rate determined by its eight day half-life. Actually, half the original amount of isotope taken up by the gland is found at between four and seven days, with an average age of six days. This shorter "effective half life" establishes the actual rate of radiation. This "effective half life" has to be determined experimentally for each individual patient by making weekly measurements of thyroid gland radioiodine content and plotting the disappearance rate.

The factor 160 in the formula is the calculated radiation in equivalent roentgens when one microcurie of I^{131} remains in 1 Gm. of tissue for total decay. This number depends on the disin-

tegration scheme of the isotope, the energy of the liberated radiations and their absorption coefficients in tissue.¹⁶ Thus the entire formula takes into account the number of microcuries deposited per Gm. of estimated gland tissue, and the "effective half life" as a correction factor to the theoretic dose calculated from the physical half life of the I^{131} .

The selection of cases for therapy was influenced by several factors. The diagnosis of toxic goiter was clear-cut and uncomplicated in all instances and was confirmed by repeated determinations of basal metabolic rate and of fasting serum cholesterol, and more recently by measurement of tracer uptake of radioiodine¹² and of serum precipitable iodine.¹⁷ However, after January, 1948, an effort was made to select patients with large glands and high toxicity of hyperthyroidism. Primary unoperated toxic goiter and toxic goiter recurrent after operation were accepted for therapy but toxic nodular goiter was avoided. No patient was accepted for therapy under twenty-three years of age, except in two instances.

CLINICAL DATA

The patients in the present study are classified into two groups, those treated prior to January 1948 and those treated from then to February 1949. An analysis has been made of each group separately and of the combined experience.

Series I. Patients Treated October, 1946, to January, 1948. This series numbered forty patients. There were twelve men and twenty-eight women. Ages ranged from eighteen to sixty-three. Twenty-four of the patients had unoperated primary toxic goiter; sixteen had a recurrence of toxicity after previous surgery. Protracted anti-thyroid drug therapy had been given without production of permanent remission to six cases.

The results of a single dose of 3 to 4 mc. I^{131} are presented in Table I. Approximately two of three patients responded to a single dose. Two were operated because it was believed unwise to delay definitive treatment and the rest were treated a second time. Retreatment was given only if remission was not observed at follow-up four months after the initial dose. Retreatment

brought the total number of remissions to thirty-three (84.6 per cent) with four more failures. One patient was lost to follow-up.

Series II. Patients Treated January, 1948 to February, 1949. This group numbered sixty-three patients. There were twelve men and

TABLE I
RESULTS OF TREATMENT OF TOXIC GOITER
WITH RADIOIODINE I^{131}

October 1, 1946–January 15, 1948		
Total number of patients	40	
Primary toxic goiter	24	
Recurrent	16	
Dosage	3–4 mc.	
	No.	Per Cent
Results after 1 dose only		
Remission	29	72.5
Failure	2	5.0
Retreated	9	22.5
Hypothyroid	0	0.0
Results after 1st and 2nd doses		
Remission	33	84.6
Failure	6	15.4
Hypothyroid	0	0.0
Lost to follow-up	1	

fifty-one women. Ages ranged from seventeen to sixty-eight. Forty-four of the patients had previously unoperated primary toxic goiter and nineteen had toxicity recurrent after surgery. Prophylthiouracil had been given over long periods without induction of permanent remission in thirteen cases.

The results of a single dosage of 3 to 6.5 mc. is shown in Table II, the size of dose given bearing a more or less direct relation to the size of the gland and toxicity of the disorder. Of the sixty-three patients in this group thirty-six were put into remission by a single treatment, one was believed too sick to warrant further uncertainty and was operated upon, two were lost to follow-up, three were made permanently hypothyroid and twenty-one were retreated. Retreatment was not given before three to four months following the initial dose. The dosage range for retreatment was the same as originally given, 3 to 6.5 mc., although in any given patient a smaller gland and decline in toxicity frequently permitted the use of smaller dosage than initially used.

The total brought into remission after one or two treatments was forty-eight (81.3 per cent). One more patient was now considered too ill to delay definitive therapy with surgery and no others were lost to follow-up. No additional patients were made hypo-

TABLE II
RESULTS OF TREATMENT OF TOXIC GOITER
January 15, 1948–May 15, 1949

	No	Per Cent
Total number of patients	63	
Primary toxic goiter	44	
Recurrent toxic goiter	19	
Average BMR	+40%	
Dosage	3–6 5 mc.	
Results after 1 dose only		
Remission	36	59 0
Failure.	1	
Retreated .	21	36 1
Hypothyroid.	3	5 0
Lost to follow-up. . . .	2	
Results after 1st and 2nd doses		
Remission . .	48	81 3
Failure.	2	
Retreated. . .	5	
Hypothyroid. . .	3	
Under observation . .	2	
(probable remission)		
Results after 1st, 2nd and 3rd doses		
Remission . .	52	89 6
Failure.	2	3 4
Hypothyroid. .	4	6 9
Under observation	3	
(probable remission)		
Lost to follow-up.	2	
Euthyroid and hypothyroid	56	96.5

thyroid. A third treatment with 3 to 6.5 mc. was given to the five patients still toxic, again not until at least three or four months had passed from the time of the second dosage. Following this final effort the final number of cases in remission was fifty-two (89.6 per cent); four (6.9 per cent) hypothyroid, and in all, two (3.4 per cent) failures. Thus, about 95 per cent of the patients in this group were relieved of toxicity.

Total Series. A summary of the total experience is shown in Table III. There were 103 cases. Twenty-four were men and seventy-nine were women. Ages ranged from seventeen to sixty-eight. Sixty-eight

represent primary toxic goiter; thirty-five had toxicity recurrent after surgery. The basal metabolic rate ranged from +12 to +76 per cent, with well over 85 per cent of the values higher than +20 per cent. The figures for treatment with an initial dose of

TABLE III
RESULTS OF TREATMENT OF TOXIC GOITER
October 1, 1946–May 15, 1948

	No	Per Cent
Total number of patients	103	
Primary toxic goiter	68	
Recurrent toxic goiter	35	
Dosage.	3–6 5 mc.	
Results after 1–3 treatments		
Remission. . . .	85	87.6
Failure. . . .	8	8.2
Hypothyroid. . . .	4	4.1
Euthyroid and hypothyroid .	89	91.7
Under observation. .	3	
Lost to follow-up .	3	

between 3 to 6.5 mc. show sixty-five (61.3 per cent) remission, three (3 per cent) hypothyroids, three (3 per cent) failures and three lost to follow-up. The results of the second and third doses are shown in Table III. The cumulative effect of the treatments show eighty-five (87.6 per cent) in remission, four (4.1 per cent) hypothyroid, eight (8.2 per cent) failures and three lost to follow-up. Three patients are still under observation. The total relieved of hyperthyroidism and either euthyroid or hypothyroid is eighty-nine (91.7 per cent).

Analysis of Results from an Initial Dose of I^{131}

Series I. An analysis of the failures in this group has been reported before.^{3,4} Large glands inevitably receive less radiation than small ones when a constant dosage of I^{131} is used. The results in this group suggested that dosages of 100/200 μ c/estimated Gm. gland of tissue and a radiation greater than 5,000 c.r. gave the best insurance of success. Gland size was noted to have returned to normal in almost every instance of successful therapy but

enlargement generally persisted in the case of failure.

Series II. This group was treated with varying dosage in an attempt to provide 100–200 μ c. per estimated Gm. of tissue and thus approximate 5,000 e.r. as suggested by

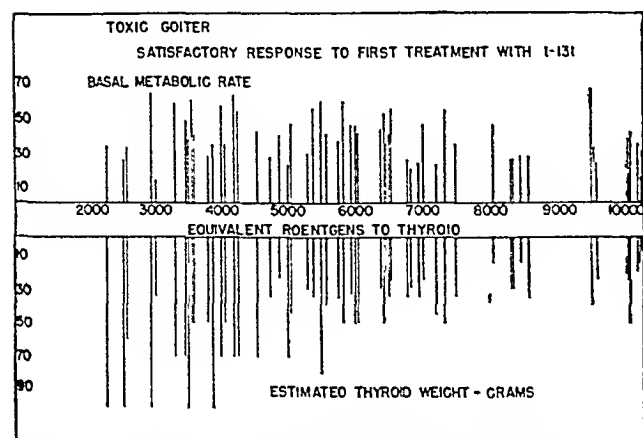


FIG. 1. Graph showing basal metabolic rate and gland size before I^{131} therapy and total radiation received in patients entering remission after a single treatment.

the analysis of results from Series I. A limit of 6.5 mc. was set, however, despite gland size (see "Methods").

TABLE IV
TABLE OF DOSAGE RANGE TREATMENTS
SINCE JANUARY 15, 1948

Dose	Remission	Failure
6.5 mc.	0	1
6.0	6	1
5.5	7	2
5.0	18	5
4.5	9	2
4.0	9	13
3.5	7	1
3.0	3	3

The successful and unsuccessful results of a single dose of I^{131} in this second series have been correlated with the dosage per estimated Gm. of gland tissue and with the radiation received by the entire thyroid. (Tables IV to VI; Figs. 1 and 2.) It is readily seen that the initial goal of dosage was only roughly achieved and that an even wider range of radiation resulted. The variability in gland uptake and in "effective" half life accounts for much of the latter. It is evident that there is no great difference in the dosage per estimated Gm. of gland or radia-

tion received between those patients brought into remission or those representing failure of treatment.

Gland size almost uniformly returned to normal with remission and not with failure. However, gland size was not entirely reduced in 8 per cent of successfully treated patients.

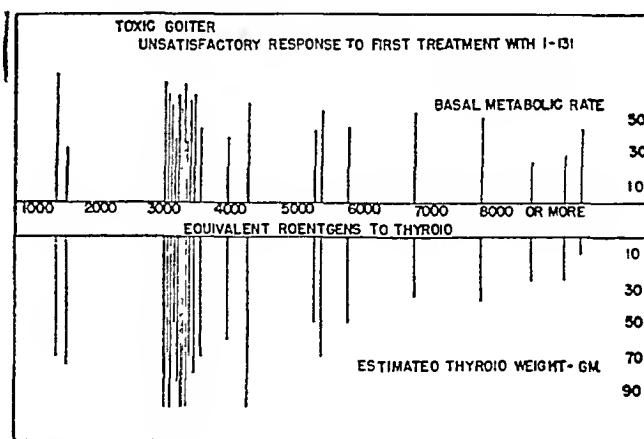


FIG. 2. Graph showing basal metabolic rate and gland size before I^{131} therapy and total radiation received in patients not entering remission after a single treatment.

TABLE V
TABLE OF DOSAGE PER ESTIMATED GM. OF GLAND WEIGHT
TREATMENTS SINCE JANUARY 15, 1948

Dose/Estimated Gm.	Remission	Failure
300–349	1	0
250–299	3	1
200–249	4	1
150–199	5	4
100–149	22	6
50–99	22	16
0–49	1	1

TABLE VI
TABLE OF EQUIVALENT ROENTGENS
TREATMENTS SINCE JANUARY 15, 1948

E.R.	Remission	Failure
10,000 up	5	3
9,000–9,900	3	1
8,000–8,900	6	1
7,000–7,900	5	1
6,000–6,900	10	6
5,000–5,900	9	5
4,000–4,900	8	5
3,000–3,900	8	4
2,000–2,900	4	1
1,000–1,900	1	1

Complications after I¹³¹ Therapy

The incidence of major complications following I¹³¹ therapy in the series of patients treated since January, 1948, is shown in Table VII.

Hypothyroidism. No critical level of dosage was found at which hypothyroidism

TABLE VII

TABLE SHOWING INCIDENCE OF MAJOR COMPLICATIONS FOLLOWING I¹³¹ TREATMENT, SINCE JANUARY 15, 1948

Hypothyroidism	
Permanent.....	4
Transient.....	3
Diplopia and orbital edema.....	2
Heart failure after therapy.....	1

could be avoided and remission of toxicity insured. Permanent hypothyroidism occurred at 11,800, 8,200, 7,700, 2,690 e.r. and with 230, 110, 65, 35 μ c/estimated Gm. of gland tissue. Hypothyroidism, clinically evident and with appropriate laboratory findings, occurred transiently about the third month after therapy and cleared by the fourth month or so in seven patients given a wide range of dosage and of radiation. However, one patient still hypothyroid six months after I¹³¹ dosage was given thyroid orally for the next six months and was found to have regained normal thyroid function upon stopping thyroid medication.

Thyroiditis. Tenderness and pain over the thyroid in the first few weeks after therapy occurred in three instances. However, a very firm feel to the gland may be noted in most instances one month after therapy, giving way to a softer consistency as the gland decreases in size. It becomes normal in consistency usually by four months after therapy, if still palpable.

Tracheitis and Laryngitis. Cough and hoarseness of the voice was noted in the first series of cases but not in the second group. The reason for this discrepancy is not clear.

Parathyroid Tetany. No instance of injury to the parathyroids was noted, clinically.

Exophthalmos. Care was taken to avoid cases suggestive of thyrotrophic, malignant, ophthalmoplegic exophthalmos. Significant advance in exophthalmos was observed in only two instances and occurred by the first month after therapy. It was associated

with diplopia and mild chemosis. Treatment with desiccated thyroid was instituted in each instance with arrest of the eye changes, if not actual improvement, although whether this was coincidental or was cause and effect is not apparent.

Transient Exacerbation of Toxicity. A flare-up in toxicity, exactly similar to that seen after x-ray therapy, has been observed. The serum precipitable iodine was studied^{18,19} and could be shown to rise concurrent with this exacerbation of hyperthyroidism.

Heart Failure. The appearance of heart failure as a result of flare-up of toxicity has not been observed. However, one patient developed heart failure during the first eight months of unsuccessful dosage but refused surgery and was finally controlled by a third dose of I¹³¹. Two patients with heart failure have been treated successfully with I¹³¹.

COMMENT AND CONCLUSIONS

It is clear that internal radiation with I¹³¹ offers a simple, highly effective method of treating toxic goiter. The results have been consistently good in all series so far reported^{5,15,20-24} and enough patients have been treated to permit a sound appraisal. I¹³¹ therapy has one great advantage over surgery. It avoids the severe complications which occasionally result from operation, such as recurrent laryngeal nerve injury and tetany. It has the disadvantage that an average of six to eight weeks may elapse from the time of treatment until remission is induced during which time the patient continues to be toxic. Also, an initial dosage does not insure a greater than two in three chance of remission. Thus, a second or third treatment may be necessary, each time with several more months of persistent toxicity although this generally becomes progressively milder with each dose. These objections to I¹³¹ therapy are, however, relatively minor. Most patients would undoubtedly be treated in this way were there not another and major obstacle to its general application. It is feared by some that later malignancy may be induced in the thyroid as a

result of the effects of a radioactive agent. It has been shown by radioautography²⁵ that there is an irregular collection of the isotope within the thyroid gland following administration. This has suggested that some cells may receive disproportionate and undue radiation during radioiodine therapy. This uneven radiation, it is held, makes it likely that malignant degeneration in the gland may appear fifteen to twenty years hence.

On the other hand, such malignant change has not apparently been noted following this interval after external radiation therapy of the gland by x-rays.²⁶ Moreover, as pointed out by Dr. Robley Evans,²⁷ it is generally a chronic radiation of low intensity which is associated with the development of later malignant change and not the brief and much more intense radiation provided by I^{131} . Despite these arguments in favor of and against the likelihood of later malignancy following I^{131} therapy, the issue has not been settled and remains conjectural. One approach to the problem has been to limit treatment of uncomplicated toxic goiter, with I^{131} to patients in the older age groups, forty-five years or over.²⁴ Survival much beyond twenty years is unlikely and hence the seriousness of later cancer formation is greatly minimized. This program allows for continued experience with the isotope and permits definitive therapy of the complicated case, such as the cardiac in whom surgery is inadvisable. However, rigid restriction to the age limit of forty-five is probably inadvisable. The younger patient who refuses surgery, or is not suitable for it and who is not brought into remission by external radiation or chronic therapy with antithyroid drugs probably should be given the benefit of I^{131} since this method will almost certainly induce remission. On the other hand, the adolescent age group and younger, i.e., from about age twenty, probably should not be treated under any circumstance in the present state of knowledge.

The above discussion holds for primary, previously unoperated toxic goiter. The

problem of radioiodine therapy for toxic goiter recurrent after operation is different. Here, unlike the situation with primary hyperthyroidism, a marked superiority of therapy with I^{131} over surgery has been demonstrated. Moreover, the other methods of treating primary goiter are found to be far less effective in the instance of recurrent hyperthyroidism than they are in the previously unoperated disease. Thus recurrent toxic goiter probably should be treated by preference with I^{131} since its greater efficacy would appear to outweigh the theoretic objections to its use.

To establish this point a rough comparison of the results after I^{131} with those after other modalities is presented. Radioiodine apparently produces the same 90 per cent ultimate remission rate in recurrent toxic goiter as it does in primary hyperthyroidism. This plus a 7 per cent incidence of hypothyroidism makes a total of 97 per cent of hyperthyroid patients relieved of toxicity, whether recurrent or not. A second surgical procedure on the other hand, once toxicity has recurred, is generally conceded to be only about 50 per cent effective, while a third operation is perhaps even less effective.²⁸ This is apart from the sharply increased technical difficulty of reoperation and the added risk of serious complications such as injury to the recurrent laryngeal nerve and parathyroid glands, and other well recognized complications.

The reports concerning external radiation with x-ray have not been specifically analyzed for its effectiveness in recurrent toxic goiter. However, everyday experience indicates that the efficacy of the method in recurrent goiter is not better than the 60 to 80 per cent remission rate achieved in primary unoperated toxic goiter^{29,30} and appears to be even less. Protracted therapy with antithyroid drugs is surprisingly ineffective in recurrent toxic goiter and is considerably less than the 40 to 60 per cent remission rate generally obtained in the previously unoperated group.^{31,32}

There is no apparent dividing line in amount of administered dosage, dosage per

estimated Gm. of gland weight, or radiation received by the gland which distinguishes successful therapy from failure. There is considerable overlap in the distribution curves of all these factors for those patients entering remission and those failing to do so. It is nevertheless a fair generalization that patients with high toxicity and large glands usually require larger initial as well as total dosage than do those with lesser toxicity and smaller glands. Similarly the amount of dosage and of radiation which will prevent hypothyroidism cannot be defined.

What the factors are which condition gland tissue responsiveness to internal radiation have not been completely elaborated. Presumably vascularity and distribution of colloid play an important role. The over-all result after such therapy is gland shrinkage and subsequent fibrosis although this may be surprisingly little for the first year after treatment.³³

Since the efficacy of I^{131} therapeutically is dependent upon an adequate uptake of the isotope by the thyroid, agents blocking such uptake must be avoided. Thus antecedent stable iodine whether administered as sodium iodide or Lugol's solution or as an organic iodine compound during intravenous pyelography or with gallbladder dye will block iodine uptake.¹² In general, two weeks without stable iodine after brief periods of such therapy, or four weeks following more prolonged administration, will suffice to permit I^{131} to be given successfully. Similarly, preceding antithyroid drug administration will block I^{131} uptake.¹² This effect may wear off in one to four days but may require several months before uptake again becomes sufficient to permit treatment with the isotope.

The incidence of malignant thyrotrophic exophthalmos after I^{131} therapy deserves mention. This complication has been seen at the Presbyterian Hospital following chronic treatment with antithyroid drugs and is well known after surgery. It is apparently not a particular hazard of external radiation therapy although eye changes have been noted after the use of I^{131} , both

in the present series and elsewhere.³⁴ These changes have been relatively mild in the present experience and became arrested before much advance occurred. This halt in progression was associated with the administration of thyroid but may have been spontaneous. Since all modalities of treatment for toxic goiter entail the risk of subsequent malignant exophthalmos, except possibly x-radiation, there is no particular choice between the other methods and I^{131} in this respect, at least according to present information. However, definitive therapy for the hyperthyroid aspect of the syndrome probably should be avoided where malignant exophthalmos appears a likely aftermath, unless relief of toxicity becomes absolutely necessary. If I^{131} then should be employed, smaller dosage than usual is probably advisable. This may avoid too sharp and rapid a reduction of circulating thyroid hormone, with consequent release of excess thyrotrophin by the anterior pituitary, a possible cause for worsening of malignant exophthalmos according to the pituitary concept of pathogenesis.³⁵

The treatment of toxic nodular goiter with I^{131} has been avoided in the present series, with one or two exceptions. The incidence of complicating malignancy in a nodular goiter with hyperthyroidism is extremely low. Nevertheless, a nodule represents a complication of hyperthyroidism and therefore surgery would seem to be the treatment of choice. Crile has found this type of goiter to be unusually resistant to I^{131} , requiring unusually high dosages of the isotope to establish remission.²⁴

Finally, the transient flare-up in toxicity which may follow I^{131} therapy deserves note. This is a real increase in hyperthyroidism and is associated with a rise in serum precipitable iodine titer.¹⁹ As a consequence, there exist the possibilities of cardiac failure and of the onset of arrhythmia. These should be watched for. Also there is a definite awareness by the patient of the exaggerated toxicity and increasing anxiety becomes apparent. Warning of the possibility of this event may help a little in tiding the patient

over this period. Studies are now in progress to establish whether stable iodine or anti-thyroid drug administered subsequent to I^{131} therapy may not avoid this complication without at the same time interfering with the efficacy of the isotope.

SUMMARY

1. The results of I^{131} therapy for toxic goiter are presented. One hundred three patients were treated with dosage between 3 to 6.5 mc.

2. The method used and the calculation of radiation are outlined.

3. The results are analyzed in terms of number of treatments, total dosage per treatment, dosage per estimated Gm. of thyroid tissue and radiation received by the gland. About 92 per cent of all the patients were relieved of hyperthyroidism; about 97 per cent in those treated more recently.

4. The use of radioiodine therapy in primary previously unoperated goiter should be restricted in general to the older age groups.

5. I^{131} is the method of choice in treating recurrent toxic goiter, when hyperthyroidism has reappeared after surgery.

6. The important complications affecting I^{131} therapy are discussed.

REFERENCES

- HERTZ, S. and ROBERTS, A. Radioactive iodine in the study of thyroid physiology: use of radioactive iodine therapy in hyperthyroidism. *J. A. M. A.*, 81: 131, 1946.
- HAMILTON, J. G., SOLEY, M. H. and EICHHORN, M. B. Deposition of radioactive iodine in human thyroid tissue. *Univ. California Publ. Pharmacol.*, 1: 339, 1940.
- WERNER, S. C., QUIMBY, E. H. and SCHMIDT, C. Clinical experience in diagnosis and treatment of thyroid disorders with radioactive iodine; eight day half life. *Radiology*, 51: 564, 1948.
- WERNER, S. C., QUIMBY, E. H. and SCHMIDT, C. The clinical use of radioactive iodine. *Bull. New York Acad. Med.*, 24: 549, 1948.
- WERNER, S. C., QUIMBY, E. H. and SCHMIDT, C. Brookhaven Conference Report on Radioiodine, Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
- CHAPMAN, E. M. and EVANS, A. D. The treatment of hyperthyroidism with radioactive iodine. *J. A. M. A.*, 131: 81, 1946.
- SEIDLIN, S. M., MARINELLI, L. D. and OSHRY, E. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. *J. A. M. A.*, 132: 838, 1946.
- CHAPMAN, E. M., SKANSE, B. N. and EVANS, R. D. Treatment of hyperthyroidism with radioactive iodine. *Radiology*, 51: 558, 1948.
- QUIMBY, E. H. Brookhaven Conference Report on Radioiodine. Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
- FEITELBERG, S. Brookhaven Conference report on Radioiodine. Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
- STANLEY, M. M. and ASTWOOD, E. B. The accumulation of radioactive iodine by the thyroid gland in normal and thyrotoxic subjects and the effect of thiocyanate on its discharge. *Endocrinology*, 42: 107, 1948.
- WERNER, S. C., QUIMBY, E. H. and SCHMIDT, C. J. The use of tracer doses of radioactive iodine, I^{131} , in the study of normal and disordered thyroid function in man. *J. Clin. Endocrinol.*, 9: 342, 1949.
- OSHRY, E. and SCHMIDT, C. Brookhaven Conference Report on Radioiodine. Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
- Unpublished data.
- SOLEY, M. H., MILLER, E. R. and FOREMAN, N. Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
- MARINELLI, L. D., QUIMBY, E. H. and HINE, G. J. Dosage determination with radioisotopes; practical considerations in therapy and protection. *Am. J. Roentgenol.*, 59: 260, 1948.
- BARKER, S. B. Determination of protein bound iodine. *J. Biol. Chem.*, 173: 715, 1948.
- HAMILTON, H. and WERNER, S. C. Unpublished data.
- RIGGS, D. S. Elevation of serum protein bound iodine after large doses of radio-active iodine. *Federation Proc.*, 7: 251, 1948.
- CHAPMAN, E. M. Brookhaven Conference Reports on Radioiodine. Brookhaven Nat. Lab. Assoc. Univ., July, 1948.
- MILLER, E. R., SOLEY, M. H. and DAILEY, M. E. Preliminary report on the clinical use of radioactive iodine I^{131} . *Am. J. Roentgenol.*, 60: 45, 1948.
- PRINZMETAL, M., AGRESS, C. M., BERGMAN, H. C. and SIMKIN, B. Toxic goiter. *J. A. M. A.*, 140: 1082, 1949.
- CRILE, G., MCCULLAGH, E. P. and GLASSER, O. Experience with radioactive iodine in the treatment of hyperthyroidism. *Cleveland Clin. Quart.*, 16: 1, 1949.
- HAINES, S. F., KEATING, F. R., POWER, M. H., WILLIAMS, M. D. and KELSEY, M. P. The use of radioiodine in the treatment of exophthalmic goiter. *J. Clin. Endocrinol.*, 8: 813, 1948.
- LEBLOND, C. P., TERTMAN, M. B., PUPPEL, I. D. and CURTIS, G. M. Radioiodine autography in studies of human goitrous thyroid glands. *Arch. Path.*, 41: 510, 1946.
- QUIMBY, E. H. and WERNER, S. C. Late radiation effects in roentgen therapy for hyperthyroidism. *J. A. M. A.*, 140: 1046, 1949.
- CHAPMAN, E. M. Personal communication.
- SLOAN, L. W. Unpublished Data.
- BJORNEBOE, M. Re-examination of 79 x-ray treated patients 8-18 years after their discharge. *Acta med. Scandinav.*, 117: 15, 1944.

30. MENVILLE, L. J. Radiologic aspect of thyrotoxicosis. *Radiology*, 18: 568, 1932.
31. WILLIAMS, R. H., ASPER, S. P. and ROGERS, W. F. Persistence of remissions of thyrotoxicosis after cessation of Thiouracil Therapy. *New England J. Med.*, 236: 737, 1947.
32. ARANOW, H., ELLIOTT, R. H. E., FRANTZ, V. K., MEICHER, G. W. and WERNER, S. C. Thiouracil in the treatment of thyrotoxicosis. *Ann. Surg.*, 124: 167, 1946.
33. CHAPMAN, E. M. Personal communication.
34. CHAMBERLAIN, R. Discussion. *Am. Radium Soc.*, June, 1949.
35. SMELSER, G. A comparative study of experimental and clinical exophthalmos. *Am. J. Ophth.*, 20: 1189, 1937.

Effect of Adrenocorticotrophic Hormone (ACTH) on Rheumatoid Arthritis*

CHARLES RAGAN, M.D., ALBERT W. GROKOEST, M.D. and RALPH H. BOOTS, M.D.

New York, New York

THIS report deals with observations on eight patients with rheumatoid arthritis who have been treated with adrenocorticotrophic hormone (ACTH). The dramatic symptomatic response of patients with rheumatoid arthritis to the administration of ACTH described by Hench et al.¹ has been amply confirmed.

An understanding of the mechanism of this response or, in fact, of the mechanism of the activity of rheumatoid arthritis has not yet been found. Before the advent of cortisone and ACTH for clinical usage any decrease in activity of rheumatoid arthritis, when it occurred, took place gradually. With ACTH, and as reported by Hench with cortisone,¹ a rapid and complete deferescence of activity takes place and activity usually returns when the medication is discontinued. This type of response suggests that the primary cause of the disease may not be affected by the administration of cortisone or ACTH, the effects being only on those factors which constitute the reaction of the host to the mechanisms that initiate and sustain the disease. These secondary factors constitute what is vaguely termed "activity" of the disease. Some of them are purely subjective, such as pain, easy fatigability, lassitude and general malaise. Others are objective and capable of measurement, such as the inflammation of the joints, rapid erythrocyte sedimentation rate, fever and anemia.

Most of our studies to determine the mode of action of ACTH in rheumatoid arthritis gave negative results. The data are recorded to save repetition on the part of

subsequent workers on this problem. A few possible leads as to the mechanism of action are presented but these require more extensive study and confirmation.

CLINICAL DATA

Plan of Treatment. Eight patients with rheumatoid arthritis have been treated with ACTH. All received the hormone intramuscularly in divided doses every six hours, save for one woman, aged sixty-two, who was treated for seventeen weeks. At the start this woman received 60 mg. a day. An attempt was made to discover the lowest dose capable of inducing remission. With 5.0 mg. three times a day, pain and stiffness recurred. With 10 mg. twice a day she was relatively free of activity. She was maintained on 20 mg. a day in two doses for six weeks, then treatment was stopped for thirty-six hours when symptoms of muscle aches, stiffness and joint pains recurred; treatment with 25 mg. a day in two doses was then resumed. One man, aged thirty-nine, received ACTH for twenty-seven days. He remained in remission on the initial dose of 60 mg. a day for six days. This was reduced to 40 mg. a day for eleven days, and then to 30 mg. a day for seven days. On dosages of 15 mg. a day for three days symptoms recurred in a mild form. The remainder of the patients were three men aged forty-three, forty-five and forty-nine, and three women, eighteen, thirty-four and forty. These patients received six to ten days of treatment with 40 mg. of ACTH daily, with an initial daily dose of 100 mg. Two of these patients received a second course of six and

* From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital, New York, N. Y. Aided in part by a grant from the Masonic Foundation for Medical Research and Human Welfare.

seven days following a twenty-one-day interval without the hormone. The age of the patient, the duration of disease in each and the duration of ACTH treatment are shown in Table 1.

Subjective Response. The dramatic clinical response of the patient with rheumatoid

TABLE 1
CLINICAL CHARACTERISTICS AND PLAN OF TREATMENT OF
EIGHT PATIENTS WITH RHEUMATOID ARTHRITIS TREATED
WITH ACTH

Patient	Sex	Age	Duration of Rheumatoid Arthritis (yr)	Other Complicating Diseases	Duration of ACTH Treatment	Average Daily Dose (mg)
W. O. T.	M	45	12	Amyloid Hay fever	2 courses of 6 days	40
P. I.	F	18	4	None	2 courses of 7 days	40
M. G.	F	40	18	None	13 days	40
A. A.	M	39	1	None	27 days	40
M. M.	F	62	14	None	17 weeks	20-25
F. I.	F	34	1*	None	6 days	40
N. M.	M	43	2½	None	7 days	40
G. M. S.	M	49	11	Ureteral calculus Bronchectasis	7 days	40

arthritis to the administration of ACTH has been confirmed with no exceptions. The improvement is rapid, as Hench¹ has stated, with relief of stiffness within twelve to twenty-four hours followed rapidly by a decrease in pain. The sedimentation rate fell markedly in all of our patients. We have been impressed with the rapid improvement in all clinical aspects of the disorder, joint inflammation and swelling, muscular stiffness and protective spasm, fever and tachycardia, but the most rapid change has been in the skeletal muscle component. In all patients studied the relief of stiffness after inactivity— notably on arising in the morning— has been noteworthy.

In all but one patient, a return of activity occurred promptly when the medication was discontinued. The exception was in a woman whose euphoria developed into a mania which persisted for eleven days after ACTH was discontinued and was terminated by electroshock therapy. Twenty-five days after ACTH was discontinued, joint pain was minimal although the erythrocyte sedimentation rate had risen slightly. The

relapse in the other cases was brisk and violent and appeared within twelve to twenty-four hours of discontinuance of the drug. For a period of four to ten days following cessation the arthritis was as severe as or worse than pretreatment. However, following this violent relapse there was a period of return of well being during which some of the improvement gained during treatment was maintained.

Subcutaneous Rheumatoid Nodules. We have treated two patients who presented the typical subcutaneous nodules frequently seen in patients with rheumatoid arthritis. The nodules were juxta-articular below the olecranon process. One patient, M. M., had had a nodule removed in October, 1948, from the left forearm. This had the microscopic appearance of a typical rheumatoid nodule.² On the right elbow a similar nodule was present which, when treatment with ACTH was started on May 24th, was approximately the same size as that removed in October from the left. After two weeks of treatment the nodule on the right was felt to be smaller and apparently was fragmenting, as several smaller nodules could be felt. These continued to decrease in size and on June 29th, after thirty-five days of ACTH treatment during which the patient continued in remission, the nodule was removed with the olecranon bursa. The synovial surface of the bursa contained several projections which the surgeon thought were villi but on section these proved to be rheumatoid nodules with large central areas of fibrinoid necrosis surrounded by dense collagen in which were palisaded rows of large mononuclear elongated cells, similar histologically to the nodule removed before treatment with ACTH. In the area of collagen many thick-walled capillaries were seen and many fibroblasts and epithelial cells. Only occasional lymphocytes could be identified and these were less in number than in the first nodule removed before treatment. One other patient presented juxta-articular nodules on both elbows which grew much smaller on ten days' treatment with ACTH.

Flexion Contractures. It has been held that the flexion contractures which occur in a large number of patients with rheumatoid arthritis result from two factors: (1) intrinsic disease of the skeletal musculature and (2) a process secondary to muscle splinting of painful joints.³ The more powerful flexor groups overcome the weaker extensors. In our experience, using slow-acting curare preparations, flexion contractures of recent origin may be overcome by depressing the myoneural junction.⁴ With ACTH a similar but much more dramatic and less evanescent effect on flexion contractures was observed. Those of recent origin promptly returned to full extension. Those of longer duration (some five years) showed evidence of increasing extension. In these we have not continued treatment long enough as yet to state whether or not full extension may be regained but the results are definitely encouraging. Improvement was most marked in the flexion contractures, which apparently do not return as rapidly as does the symptomatic relapse or the laboratory relapse.

Heart Size. Two of the eight patients have shown a definite increase in heart size while on treatment with ACTH. No significant increase could be detected in the other six. In one patient this increase was approximately 2 cm. and was not modified by sodium restriction. The second patient showed an increase of 1.9 cm. in a six-day period of treatment with a weight gain of 3.4 Kg. On a subsequent course of ACTH for six days with fairly rigid sodium restriction there was no weight gain, an increase in heart size of only 0.5 cm. occurred and there was no decrease in hematocrit. In the other patients sodium was not restricted and slight hemodilution, as measured by hematocrit, was noted in five of six patients studied.

CHEMICAL CHANGES

Sodium and Potassium. Changes in sodium and potassium excretion have been described following the administration of ACTH.^{5,6} Balance studies were made in

one of our patients, A. A. This patient was maintained on a constant diet and twenty-four-hour urine sodium and potassium determinations were made, using the flame photometer.* With 60 mg. of ACTH daily there was marked retention of sodium and a minimal increase in potassium excretion. This was not mirrored in the serum sodium or potassium which changed relatively little but was associated with a weight gain of 3 Kg. When the ACTH was cut to 40 mg. per day, after six days at a dosage of 60 mg., there was a slight sodium diuresis and the gain in weight continued at a slower pace. However, the arthritis continued in remission. After eleven days at a dosage of 40 mg. the dose was decreased to 30 mg. and there was a considerable sodium diuresis with a loss of 2.2 Kg. in weight, which reached the pretreatment level. The arthritis continued in remission. After seven days at a dosage of 30 mg. the dose was reduced to 15 mg. and there was a marked sodium diuresis with weight loss to 1 kilogram below pretreatment levels. The arthritis was in partial but not complete remission although the erythrocyte sedimentation rate (ESR) remained low. After three days on a dosage of 15 mg. the drug was discontinued and in the next twenty-four hours there was a one-day diuresis of sodium followed by no further weight loss but with a very prompt return of symptoms, rise in ESR and fever.

All eight patients with rheumatoid arthritis whom we have treated have gained weight temporarily on ACTH. This weight gain has been between 1 and 4 Kg.

One patient developed a low serum potassium, 2.7 m.Eq./L. (pretreatment 4.4), after thirteen days on ACTH. Subsequently, after sixty days' treatment at a dosage of 25 mg. the serum potassium remained at about 3.7 to 3.9 m.Eq./L. while ingesting 1.8 Gm. of potassium chloride in addition to her diet. There were no symptoms associated with the low potassium level. The serum sodium concentration varied con-

* We are indebted to Dr. Kermit Pines for these determinations.

siderably and did not mirror weight changes or hemodilution.

Uric Acid Excretion. An increased excretion of uric acid has been described following the administration of ACTH.⁵⁻⁹ We have followed urinary uric acid in two

After treatment was discontinued there was a slight fall. In the other patient there was apparently a definite but small rise in uric acid excretion which decreased when medication was stopped temporarily and then rose again when ACTH was resumed.

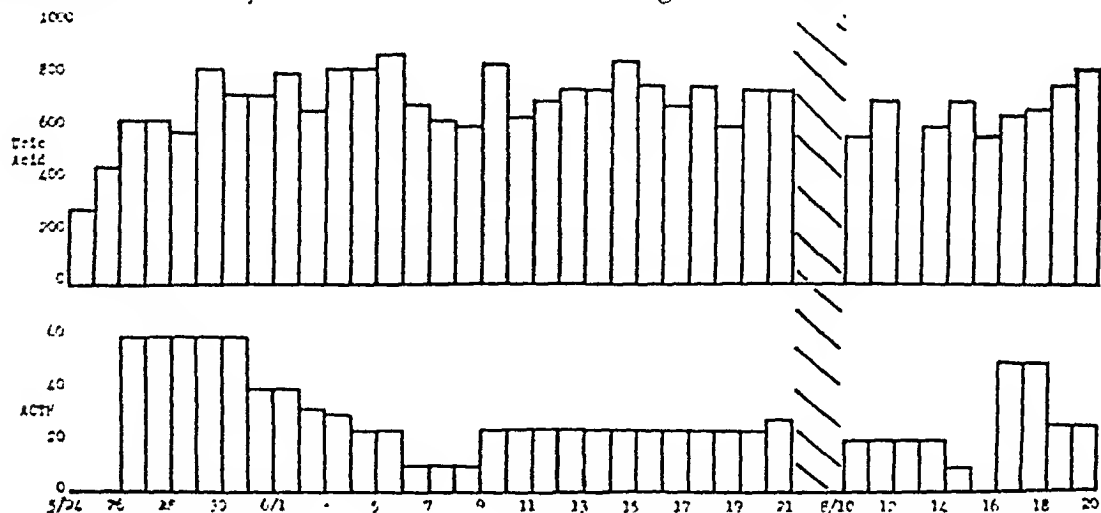


FIG. 1. Patient M. M., urine uric acid excretion. Uric acid—mg. per twenty-four hours; ACTH—mg. per twenty-four hours.

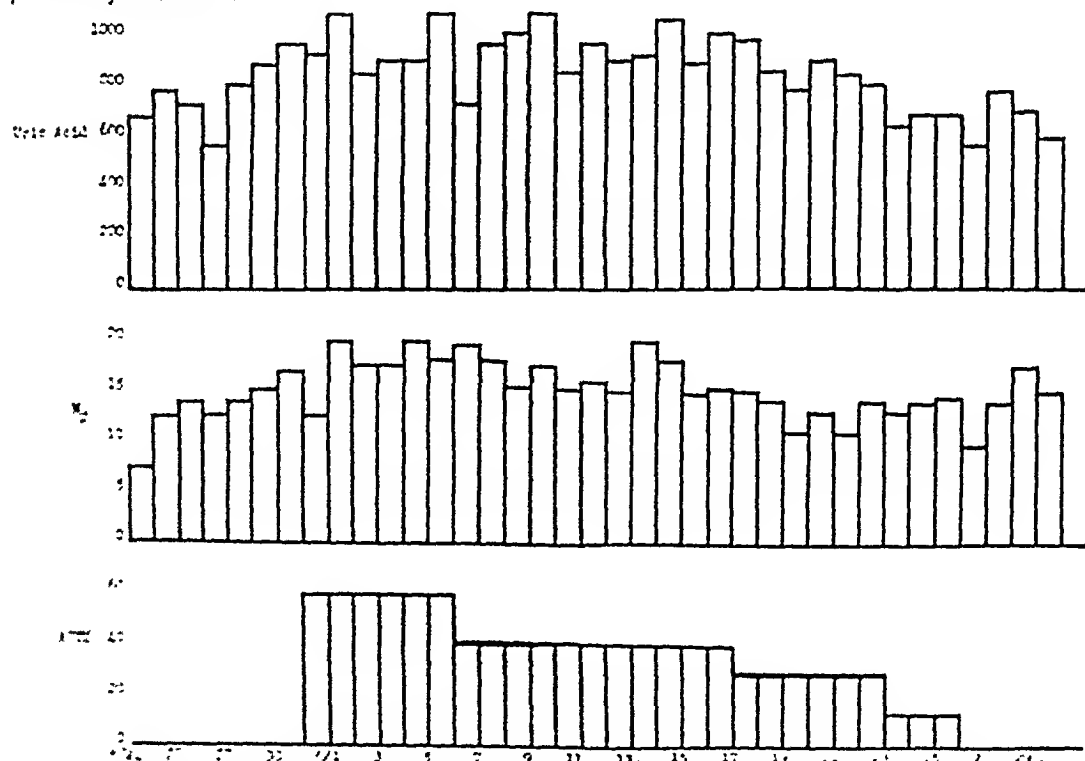


FIG. 2. Patient A. A., urine uric acid and nitrogen excretion; patient on a constant diet. Uric acid—mg. per twenty-four hours; nitrogen—gm. per twenty-four hours; ACTH—mg. per twenty-four hours.

patients (Figs. 1 and 2.) In one, fever in the control period may have masked any significant rise during the period of treatment.

Urine Nitrogen Excretion. An increase in urine nitrogen excretion has been described following the administration of ACTH.⁵⁻⁹

This was followed in one patient on a constant diet (Fig. 2). There was a small increase in nitrogen excretion during the initial phase but this fell to control levels when the dose was decreased although clinical and laboratory remission continued.

turned to approximately pretreatment levels in two patients studied within three weeks.

Serum Proteins. The protein changes described by Hench¹ have been confirmed. There is a rapid fall in ESR in all patients. In one patient with concurrent amyloidosis

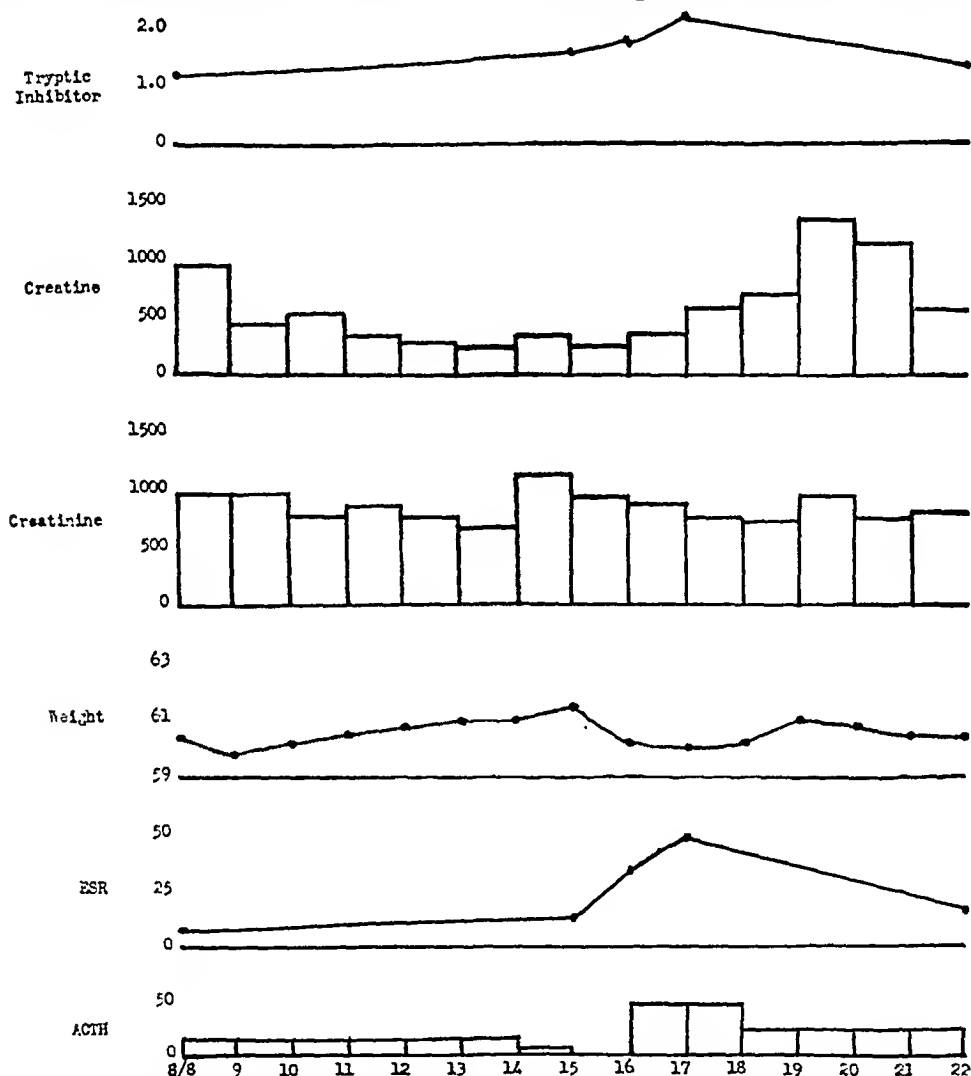


FIG. 3. Patient M. M., creatine excretion. Creatine and creatinine—mg. per twenty-four hours; weight—kg.; ESR—mm. per hour (Westergren); ACTH—mg. per twenty-four hours; tryptic inhibitor—see Table II.

Creatinuria. An increase in creatinuria following the administration of ACTH to a normal subject has been described.⁶ In two patients studied there was a large outpouring of creatine (Figs. 3 and 4) at one time during the treatment period. This increased creatinuria did not continue, however, throughout the period of treatment with its attendant remission.

Serum Inorganic Phosphorus. This was followed in all patients. At some time during treatment with ACTH there was a definite drop in serum inorganic phosphorus in six of the eight patients. (Table II.) This re-

this did not reach normal levels after treatment for a week. (Table II.) In another patient treated for six days the fall was not to normal. In all others normal levels were reached within a week. In all who have now been followed after treatment was discontinued the ESR returned promptly to levels at or above pretreatment levels. This rise occurred promptly, with some rise becoming manifest usually within forty-eight hours after medication was discontinued. In three patients followed after ten to thirty days' treatment there was a fall in total serum globulin and in euglobulin. Changes

in serum albumin were less consistent. The cephalin-flocculation test was positive in one patient and this became negative with treatment. (Table II.)

Tryptic inhibitor levels of the serum were followed using the method of Britten and

changed to doubtful, in the patient, M. G., who developed acute mania. (Table III.) The sensitized sheep cell agglutination has shown a similar variability in titer with some diminution on treatment and a return to higher titers on discontinuation of treat-

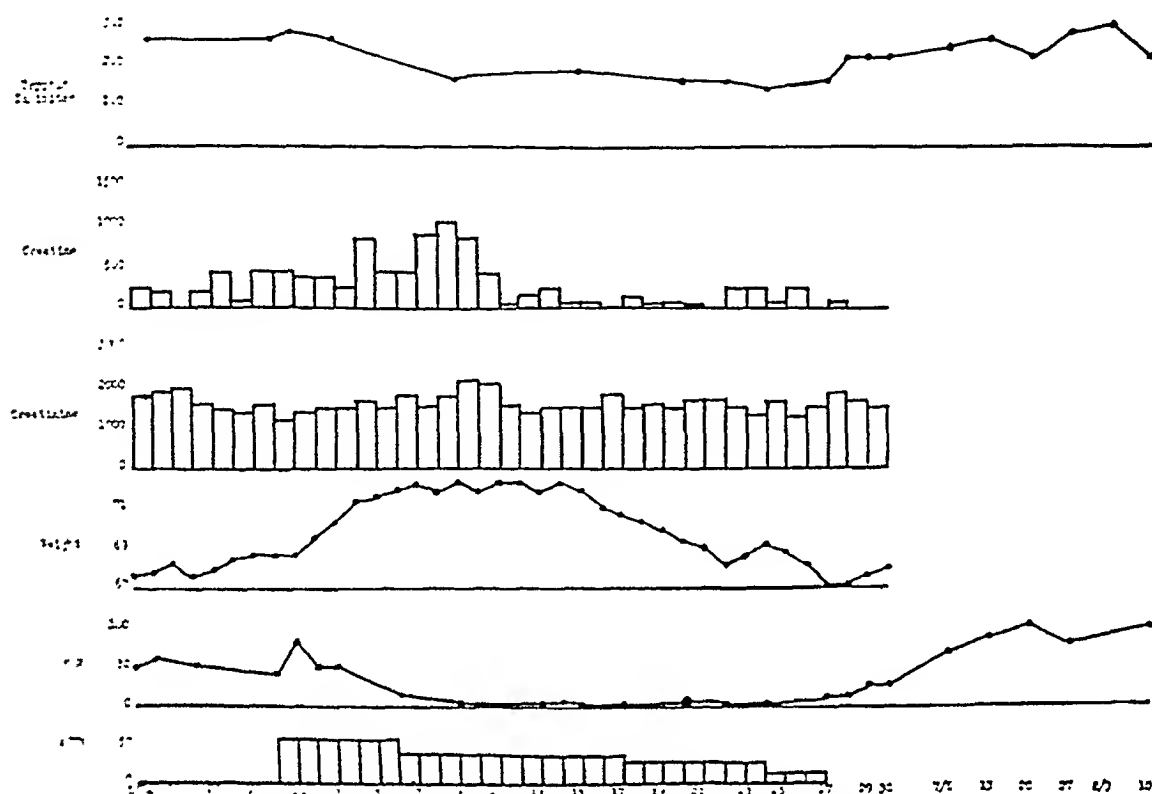


FIG. 4. Patient A. A., creatine excretion; same as Figure 3.

Clark.¹⁰ These were above the normal range in the control period in all and fell appreciably in all during treatment, to return promptly when treatment was discontinued to levels at or above those seen in the control period (Table II.) The significance of this reaction is not known.

Immunologic Changes. Approximately 50 per cent of patients with rheumatoid arthritis have in their serum an agglutinin for group A hemolytic streptococci¹¹ and about 60 to 70 per cent have an agglutinin for sensitized sheep cells.¹² These two antibodies were followed in all patients. There was some variability in the titer of the group A streptococcus agglutination but the reaction remained positive in all but one instance in which a positive agglutination

ment. (Table III.) Again, only one of eight patients showed a fall from the rheumatoid range to the normal range. This patient, M. G., had only a weakly positive titer in the control period and the fall was only of one tube. On subsequent examination, while still on ACTH, the titer was at the pretreatment level. Since treatment was maintained in one patient for ten weeks and in another for four weeks, and since other changes in serum proteins reverted toward normal and these agglutinins persisted, it is possible that these antibodies may represent an integral part of the disease and may not be secondary reactions to a chronic granulomatous process. It is also possible that for reasons unknown the reversion to normal of these serologic reac-

tions may be delayed and not take place during the period of treatment we have employed.

One patient also had an elevated anti-streptolysin-O titer. This failed to change significantly during twenty-seven days of treatment.

TABLE II
HEMATOCRIT, PROTEIN AND PHOSPHORUS CHANGES

Patient	*	Hematocrit— Per Cent Cells	Weight—Kg.	Proteins			ESR— mm. per hour Westergren	Cephalin Flocculation	Tryptic Inhibitor— mg. Equiv.†	Inorganic Phosphorus— mg. Per Cent
				Albumin— Gm. Per Cent	Globulin— Gm. Per Cent	Euglobulin— Gm. Per Cent				
W. O'T.	1	31.3	60.6	3.9	5.0	1.6	145	0	2.2	3.5
	2	27.5	63.9	3.6	3.9	0.8	90	0	1.8	3.0
P. F.	1	45.3	59.0	44	..	1.6	4.9
	2	40.8	61.0	20	..	1.2	3.4
M. G.	1	35.0	46.5	67	..	1.6	5.2
	2	38.0	47.6	5	..	1.2	2.2
A. A.	1	...	68.0	4.4	2.3	0.5	57	..	2.6	5.3
	2	...	72.3	4.4	1.7	0.	4	..	1.4	3.3
M. M.	1	...	58.1	3.6	2.1	0.	31	++	2.0	3.6
	2	...	61.4	4.1	1.7	0.	3	0	1.2	2.4
E. E.	1	...	42.3	96	++	...	3.2
	2	30.5	43.8	50	+	...	3.4
N. M.	1	42.1	69.4	76	3.8
	2	40.7	72.7	20	4.1
G. McS.	1	40.1	59.4	45	0	...	3.8
	2	36.4	60.3	14	2.8

* 1, Control; 2, during treatment.

† mg. equivalent to crystalline soya bean inhibitor when equal amounts of crystalline soya bean inhibitor and crystalline trypsin neutralize.

Cholesterol Partitions. These were carried out in seven patients. There is apparently a wide variation in the serum cholesterol of patients with rheumatoid arthritis treated with ACTH. In five of the patients the period on ACTH was relatively uneventful and in four of these there was a rise in cholesterol, both free and esterified. (Table iv.) There was no change in the fifth patient. One patient whose euphoria ended in a hypomanic or manic state showed a marked drop in total cholesterol with the percentage of esterified cholesterol falling 3 per cent. One patient had an attack of ureteral colic due to stone during the treatment period which inconvenienced him for a period of two days and this patient showed a drop in total cholesterol, again with the percentage of esterified cholesterol falling 4 per cent. The significance of these changes is not clear.

Glucose Metabolism. Changes in carbohydrate metabolism following the administration of ACTH have been observed.^{5,7} Frequent fasting blood-sugar determinations were made during the treatment period in two patients who received ACTH for relatively long periods. Both of these patients

TABLE III
IMMUNOLOGIC CHANGES

Patient	*	Streptococcus Agglutination			Sensitized Sheep Cell Agglutina- tion
		Result	Highest Titer	First Tube	
W. O'T.	1	negative	0	0	16
	2	negative	0	0	32
P. F.	1	positive	1/640	++	64
	2	positive	1/640	++	32
M. G.	1	positive	1/640	++	16
	2	doubtful	1/160	±±	32
A. A.	1	positive	1/320	++	512
	2	positive	1/160	++	32
M. M.	1	positive	1/320	++	512
	2	positive	1/320	++	64
E. E.	1	positive	1/320	++	256
	2	positive	1/320	++	1024
N. M.	1	positive	1/640	++	32
	2	positive	1/640	++	16
G. McS.	1	doubtful	1/80	±±	128
	2	doubtful	1/80	±±	64

* 1, Control; 2, during treatment.

given 60 mg. of ACTH daily showed a slight elevation in fasting blood sugar, from 85 to 120 mg. per cent. However, when the dose was lowered to 40 mg. a day, while the remission of the arthritis persisted the fasting blood-sugar levels approached those seen in the control period. Neither of these patients showed a significant glycosuria. In none of the other patients did a definite glycosuria appear. No sugar tolerance studies were carried out.

Excretion of Glucuronic Acid and Gentisic Acid. With salicylate ingestion there is a prompt rise in urine glucuronic acid¹³ and in an ether-soluble chromogen believed to be gentisic acid.¹⁴ Two patients receiving ACTH were followed for glucuronic acid and gentisic acid excretion. There was no increase in either. Thus two of the chemical

accompaniments of salicylate ingestion were not seen following the administration of ACTH.

Mental Changes. In all these patients there was some degree of the "euphoria" described by Hench.¹ It is to be noted that

TABLE IV
CHOLESTEROL PARTITIONS

Patient	*	Cholesterol—Mg. Per Cent			Ester— Per Cent
		Total	Free	Ester	
W. O.T.	1	173	52	121	70
	2	204	66	138	68
P. I.	1	158	45	113	72
	2	178	49	129	73
M. G.	1	171	46	125	73
	2	138	42	96	70
M. M.	1	195	47	148	76
	2	206	57	149	72
L. E.	1	178	49	129	74
	2	172	46	126	73
N. M.	1	204	58	146	72
	2	229	66	163	71
G. MeS.	1	269	76	184	71
	2	192	65	134	67

* 1, Control, 2, during treatment.

in two of our patients on the second course of treatment there was less of this euphoria. However, a constant finding has been a subjective sense of mental alertness, most marked at night. The patients state that they keep thinking and are unable to sleep. One patient was subjected to psychometric tests during treatment and after it was discontinued. No appreciable difference could be elicited. Electroencephalograms have been done in all.* During treatment there appears, at variable times, an abnormal EEG pattern manifested by the appearance of increasing amounts of slow (5 second) activity. This appeared in six of the eight patients and disappeared when the medication was discontinued.

Evidence of Hyperadrenism. Hench¹ has described the moon facies, striae, amenorrhea, hirsutism and acne appearing in

patients treated with cortisone and ACTH. In almost every one of our patients, upon careful search, some evidence of hyperadrenism could be detected associated with remission of the arthritis. This was manifested either as moon facies, slightly increased uric acid excretion, slight changes in carbohydrate metabolism, retention of sodium or a lowered serum potassium concentration.

COMMENTS

These patients with rheumatoid arthritis were maintained in a state of remission on ACTH.* The arthritis was completely quiescent and only irreversible changes in bones and joints remained in the relatively short periods of treatment employed. With the dosage schedule used for control of rheumatoid arthritis there was minimal sodium retention, most readily detected by a sodium diuresis following withdrawal. Increase in nitrogen and uric acid excretion was minimal. Serum inorganic phosphorus may be temporarily decreased in some of the patients. A temporary but striking creatinuria appeared with treatment. The variability in serum cholesterol follows no pattern and needs more elucidation.

Reversion of the various protein abnormalities to normal under ACTH treatment and their return to pretreatment levels upon cessation of treatment suggests that these are associated with "activity" of the disease resulting from the host response. Included in this group of disturbances are serum globulin, cephalin flocculation, ESR and tryptic inhibitor levels. Serologic findings characteristic of rheumatoid arthritis remained abnormal in all but one instance, at least for the duration of therapy we have used. The pathogenesis of these serologic changes is unknown but apparently these alone of the many clinical and laboratory findings described may persist for relatively long periods of remission induced by ACTH. It is consequently possible that these changes

* We wish to thank Dr. Paul H. Hefter for performing the psychometric tests. These results will be reported in detail in a subsequent paper.

* We wish to thank Dr. John R. Mote, Medical Director of The Armour Laboratories, Armour & Company, for the supply of ACTH.

are associated with the primary disease process and may not be secondary to it. Be that as it may, it seems apparent that the underlying disturbance continues to be present in a patient with rheumatoid arthritis maintained on ACTH in complete objective and subjective remission. In our experience when the hormone was discontinued, prompt resumption of symptoms and laboratory and clinical signs took place in seven of eight patients. It is possible that, when sustained remissions follow ACTH therapy, a spontaneous remission such as is encountered in the natural history of the disease has taken place.¹⁵

It is of interest and perhaps of importance that many patients in the course of improvement under treatment with ACTH or cortisone develop a variety of disturbances characteristic of hyperadrenalism. Thus Hench,¹ as stated above, has described the development of moon facies, striae and mild hirsutism, etc., of Cushing's syndrome. Similar changes have been observed by us. Sodium retention persisted on small amounts of ACTH. The patient maintained for seventeen weeks on ACTH developed the facies of Cushing's disease. One patient with lupus erythematosus disseminatus, who had developed moon facies, died from pulmonary infarction after three weeks of treatment with ACTH. At postmortem examination the adrenals were three times the normal size. A slight increase in uric acid excretion was found to be present during remission. It thus seems possible that in order to produce and maintain clinical remission with ACTH some measure of hyperadrenalism must be induced.

While the responses to ACTH cover a broad spectrum of metabolic changes, it is possible that the remission in rheumatoid arthritis reflects the effect of excessive amounts of adrenal steroid upon mesenchymal tissue. Three patients have been observed who apparently formed granulation tissue poorly while being treated with ACTH. The first was a patient with dermatomyositis. A muscle biopsy wound produced the day before ACTH was started

required twelve days to heal while ACTH therapy was continued. A biopsy wound made the day before ACTH treatment was discontinued healed in four days. There was only a moderate elevation of fasting blood sugar (71 to 90 mg. per cent) during treatment with ACTH. One patient with lupus erythematosus disseminatus (LED) developed severe symptoms postpartum. An episiotomy wound made at the time of delivery failed to heal but profuse granulation tissue was seen in this wound at the time we first saw her twenty-five days after delivery. She developed a decubitus ulcer shortly after ACTH was started and up to the time of her death from pulmonary infarction after eighteen days on ACTH, very little granulation tissue appeared in this ulcer. It is to be noted that up to three days before death she was making excellent progress and the symptoms of LED were controlled. The third patient was also one with LED. While under treatment with ACTH she developed a suppurative parotitis and an abscess on her back. It was necessary to incise and drain both of these. While on ACTH little or no granulation tissue appeared in either wound. After twenty-eight days on ACTH she developed a full moon facies and abdominal striae; the symptoms of LED were apparently controlled. Within twenty-four hours after cessation of ACTH, symptoms of LED returned and four days after the hormone had been stopped, granulation tissue could be seen in the wounds. No significant hyperglycemia was noted during treatment with ACTH. As a corollary to these observations may be cited the well recognized weakness of supporting tissues in Cushing's syndrome.

It has been postulated¹⁶ that rheumatoid arthritis is a disease in which the mesenchymal tissues are overactive and thus it is possible that excessive amounts of adrenal steroids may depress the activity of the mesenchymal tissues and thereby depress the host responses which cause the "activity" of the disease.

CONCLUSIONS

1. There is a striking and prompt remission of the symptoms of rheumatoid arthritis in patients treated with ACTH.

2. Following cessation of therapy in seven of eight patients there was a prompt symptomatic relapse.

3. Protein changes—serum globulin, ESR, cephalin flocculation and tryptic inhibitor levels—followed the symptomatic remission and relapse.

4. Serologic changes—agglutination of group A hemolytic streptococci and sensitized sheep cell agglutination—changed with treatment much less than protein changes and in only one instance was the change significant.

5. It seems possible that to produce a remission in rheumatoid arthritis some measure of hyperadrenalism must also be produced.

6. Evidence is presented to suggest that with hyperadrenalism there is a depression of growth of certain mesenchymal tissues, chiefly granulation tissue.

7. It is suggested but not established that the favorable response of the patient with rheumatoid arthritis to administration of ACTH is due to the production of hyperadrenalism and a consequent suppression of the activity of mesenchymal tissue.

We wish to thank the Misses E. Bidwell, G. Carleton, J. Nellenbogen, V. Pratt and K. Vislocky for technical assistance.

REFERENCES

1. HENRI, P. S., KENDALL, E. C., STOCUM, C. H. and POTTS, H. F. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis. Preliminary report. *Proc. Staff Meet., Mayo Clin.*, 24: 181, 1949.
2. DAWSON, M. H. and BOOTS, R. H. Subcutaneous nodules in rheumatoid (chronic infectious) arthritis. *J. A. M. A.*, 95: 1894, 1930.
3. DAWSON, M. H. and RAGAN, C. Chronic Arthritis. Nelson's Loose-Leaf System of Medicine. Chap. II, 1949.
4. SCHLESINGER, E. B. and RAGAN, C. "Muscle spasm" in acute low back pain and similar syndromes. *Am. J. Med.*, 1: 621, 1946.
5. FORSHAM, P. H., THORN, G. W., PRUNTY, F. T. G. and HILLS, A. G. Clinical studies with pituitary adrenocorticotropin. *J. Clin. Endocrinol.*, 8: 15, 1948.
6. MASON, H. L., POWER, M. H., RYNEARSON, E. H., CIARANELLI, L. C., LI, C. H. and EVANS, H. M. Results of administration of anterior pituitary adrenocorticotrophic hormone to a normal human subject. *J. Clin. Endocrinol.*, 8: 61, 1948.
7. CONN, J. W., LOUIS, L. H. and JOHNSTON, M. W. Alleviation of experimental diabetes in men by administration of reduced glutathione (GSH): metabolic implication. *Science*, 109: 279, 1949.
8. ROBINSON, W. D., CONN, J. W., BLOCK, W. D., LOUIS, L. H. and KATZ, J. Role of the anterior pituitary and adrenal cortex in urate metabolism and in gout. Official Program, 7th International Congress on Rheumatic Diseases. New York, 1949.
9. FORSHAM, P. H., FLINK, E., EMERSON, K. JR. and THORN, G. W. Metabolic studies on Cushing's syndrome. *J. Clin. Investigation*, 28: 781, 1949.
10. BRITTLIN, R. C. and CLARK, D. G. C. In press.
11. BOOTS, R. H., LIPMAN, M. O., COSS, J. A. JR. and RAGAN, C. Immunological reactions in rheumatoid arthritis. Official Program, 7th International Congress on Rheumatic Diseases. New York, 1949.
12. ROSE, H. M., RAGAN, C., PEARCE, E. and LIPMAN, M. O. Differential agglutination of normal and sensitized sheep erythrocytes by sera of patients with rheumatoid arthritis. *Proc. Soc. Exper. Biol. & Med.*, 68: 1, 1948.
13. MEYER, K. and RAGAN, C. Hyaluronic acid and the rheumatic diseases. *Med. Concepts Cardiovas. Dis.*, 17: 1948.
14. YU, T. F. and GUTMAN, A. B. Interference of gentisic acid in determination of urinary uric acid after administration of salicylates. *Federation Proc.*, 8: 1949.
15. RAGAN, C. The general management of rheumatoid arthritis. *J. A. M. A.*, 141: 124, 1949.
16. RAGAN, C. and MEYER, K. The hyaluronic acid of synovial fluid in rheumatoid arthritis. *J. Clin. Investigation*, 28: 56, 1949.

Some Technics for Recording the Ballistocardiogram Directly from the Body*

WILLIAM DOCK, M.D. and FELIX TAUBMAN, M.D.

Brooklyn, New York

BALLISTOCARDIOGRAPHY, the recording of motion imparted to the body by the motion of blood and the heart during each cardiac cycle, has been developed as a research method by Starr^{1,8} and others.^{3-6,10} Though the method promised to give information on the volume of blood ejected by the ventricles, it has been found unreliable under abnormal conditions since the amplitude of the waves depends on velocity rather than on volume alone. However, the curves are of value in detecting cardiac disease^{1,2,5,7-9} and coarctation of the aorta.^{2,5,6}

All of the reported work has been done by having the subject on a table which is mounted on springs to damp its motion and recording movements optically or by an electrical detecting device and an amplifying circuit. The latter is controlled to give a centimeter deflection of the galvanometer record for a standard pressure applied to the table. The tables are bulky, fixed installations and ballistocardiography today is in the same state that electrocardiography was prior to 1920. The instrument is precise and dependable but bulky, immovable and expensive.

Since ballistocardiograms seem to be of more value as empirical clinical indices of disease than for precise physiologic measurement of function, it seemed desirable to develop methods for clinical use. This proved to be rather simple, and the accessories needed for inscribing ballistocardiograms with standard electrocardiographic instruments are inexpensive and not particularly bulky. Records can easily be made in the ward, office, operating room or the home.

* From the Department of Medicine, Long Island College of Medicine, Brooklyn, N. Y. Aided by a grant from the United States Public Health Service.



FIG. 1. Sphygmographic receiver (glycerine capsule) (a) mounted on head-board with counter weight (b). The axle (c) is 6 cm. wide and 1 cm. in diameter; the counterweight is 400 gm. The axle may be set either 22 or 23.5 cm. from the base board; the receiver and counterweight are centered 15 cm. from the axle.

APPARATUS AND TECHNIC

Sphygmographic Method. We learn that several others had noted that a pressure recorder, applied to the vertex of the head, gave ballistocardiographic curves; Hamilton⁵ (Fig. 6) and Nickerson³ (Fig. 4H) have published such records. We used the standard Cambridge Simplitrol pulse recording device and applied to the head either the glycerine capsule usually employed to pick up radial or femoral pulsations, or a receiver made by mounting a cork button 3 cm. in diameter on a rubber membrane 5 cm. in diameter. Either receiving device is mounted on a rigid arm 15 cm. long, extending vertically from an axle with another arm of equal length carrying a 400 Gm. counter weight at a 90 degree angle. This is mounted, as shown in Figure 1, so that the receiving capsule or

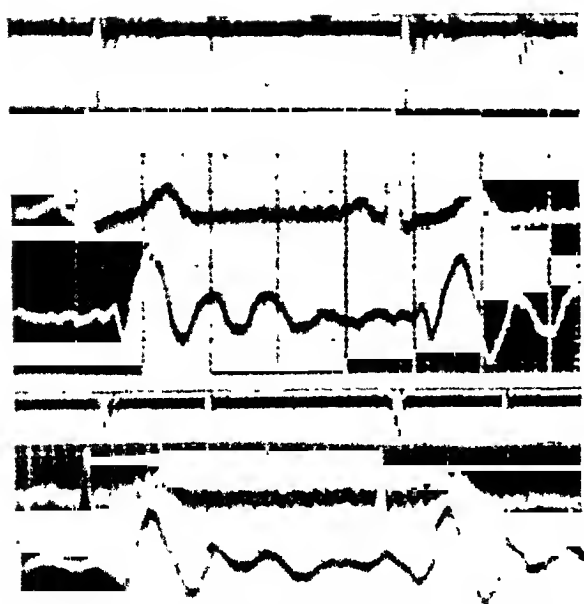


FIG. 2. Simultaneous sound, ECG and ballisto tracings made with Simplotrol.

button is held against the head with a uniform and constant pressure.

A leak in the tubing from receiving membrane to recording membrane is necessary to prevent wide respiratory swings and keep the record centered; if the leak is too large no record is inscribed. This leak is provided by a rubber tube on a Y-tube close to the recorder. It is closed with a screw clamp until release of pressure on the receiver causes a return of the shadow of the lever in 2 or 3 seconds. Another screw clamp, near this side tube but on the tube to the receiver, can be closed and gradually released until a normal subject gives oscillations of 2 cm. or more. This clamp acts as a low-pass filter and cuts out high frequency waves, either

anxious from muscle tremor, or harmonics up in the recording system. Oscillations of less than 20 per second are adequately filtered and the ballistocardiogram is faithfully reproduced. Synchronous records of heart electrocardiograms and ballistocardiograms are available (Fig. 2) to those who can tolerate the method. The time lag in the pulse is negligible while that in the electrical recording is about one-half second.

Subjects may be stiff and give no record, or, by putting them under ether, they become sensitive. The older membranes age and give no records of use. The younger subjects do not give records of head tremor

Photo-electric Method. If a piece of cardboard is firmly attached to the head and a shadow cast by its edge falls on the middle of a photocell, the electrical current recorded by the galvanometer varies with the motion of the body. When motion in the long axis of the body is recorded, the

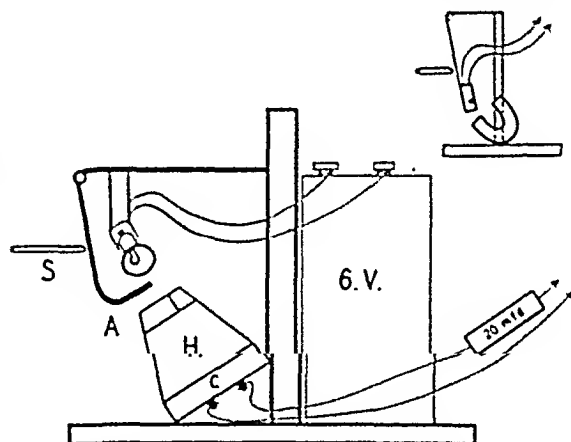


FIG. 3. Photocell ballistocardiograph with hinged occulting strip. S, strip across shins; H, hinge; C, strip casting shadow on cephalad half of the photocell, shielded by the hood. B, upper insert, Alnico magnet and coil in use as ballistocardiograph.

curves are identical with those made with the pulse recorder on the vertex. We also recorded this motion from a rigid strip of metal placed across the shins, with the legs slightly abducted and the photocell below and light source above the strip. This is possible even in orthopneic patients, and tremor of the legs is less frequent than tremor of the head. At present we use an occulting edge mounted on a hinge so that it is at a fixed distance from the bulb, and we press the hinge against the strip across the shins or against the vertex of the skull. (Fig. 3.)

We find the 890 photocell, hermetically sealed (Photovolt), gives excellent records when illuminated by a 6 volt flashlight bulb (G. E. 31). It is necessary to use a condenser (16-24 mfd) in one lead to the string galvanometer or direct writer in order to filter out or reduce respiratory movement. No amplifier is needed and there is less than 0.005 of a second time lag. The records are standard and reproducible when the galvanometer is set to give 1 cm. per millivolt deflection, and the shadow edge falls on the same part of the photocell.

The photocell and light bulb are mounted 6 cm. apart, with the cell protected from outside light by a tapered shield 3.5 cm. high. The occulting strip is 2 to 4 mm. from the bulb, and the whole apparatus is pressed toward the strip across the shins until the shadow falls on a line

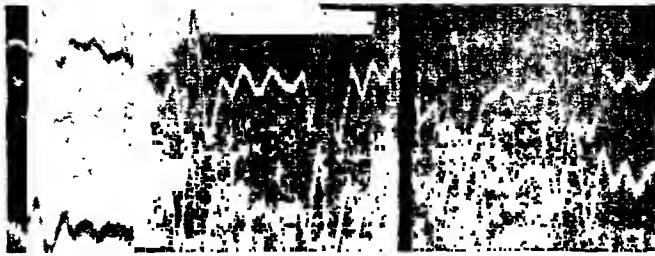


FIG. 4. Electromagnetic trace, lower, and photocell trace, simultaneous record from the shins. Note that changes in velocity (electromagnetic trace) occur 0.02 to 0.06 second before change in position becomes apparent in records A and B made without a low pass filter, while the peaks and troughs are practically synchronous in record C inscribed with the filter, in this case 100 microfarads across the leads.

marked on the light shield. Thus it falls on the same part of the cell at all times when tracings are being inscribed. The photocell terminals are connected with the arm leads of the ECG; by trial it is determined which arm lead should be attached to the condenser and which to the wire to the other pole of the cell to give an upward J wave. The terminals are then marked for right and left arm for all subsequent use.

Electromagnetic Method. When a coil of fine copper wire is substituted for the occulting strip on the hinge shown in Figure 3, and an Alnico horse-shoe magnet is mounted in place of the photocell so that the coil moves in the strongest part of the field, a galvanometer attached to the coil inscribes a ballistocardiogram when the hinge presses upon the vertex or a strip across the shins.

The relation of such curves to the photocell tracing is seen in Figure 4. The inflections precede the photocell inflections by 0.03 to 0.06 second, which is not surprising as the velocity of body motion determines the voltage of the electromagnetic current, while displacement causes the photoelectric potential changes. The electromagnetic record picks up muscular tremor of high frequency, but this can be filtered out by putting a capacitance across the leads, and inductance in one lead on either side of the capacitance. This changes the wave phase, delaying the peaks by 0.02 to 0.06 second, so that they coincide with the photoelectric wave peaks.

This is the simplest way to record the ballistocardiograph. It may be argued that it is better to record the velocity of bodily motion than the distance moved by the body; actually the curves are so much alike that the clinical significance is unchanged. Only experience in the clinic can decide which method most effectively detects abnormalities in motion of the blood.

Effect of Mattresses and Bed Casters. Records made with patients in ward beds show varying degrees of damping and distortion, as compared with those made on a fluoroscopic table or on any rigid, smooth surface. If the bed is on casters, the records may be greatly distorted.

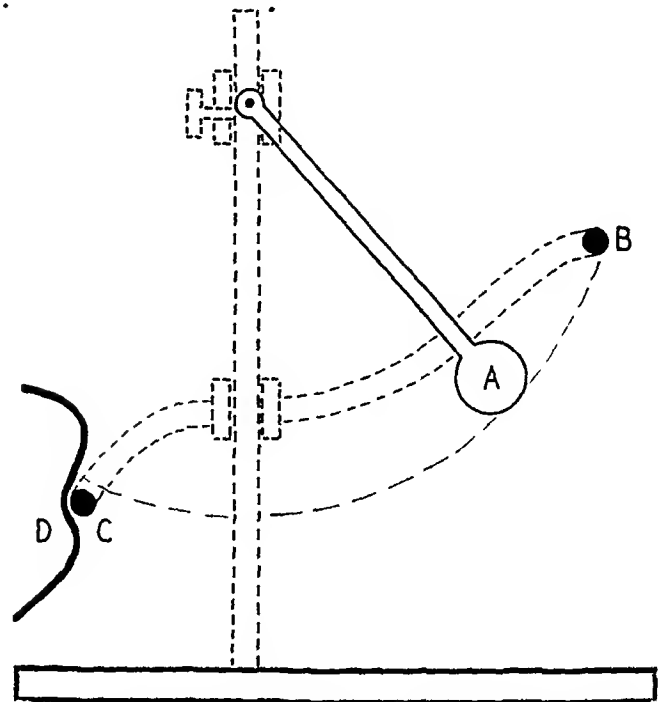


FIG. 5. Standard pendulum to deliver 200,000 dyne blow to the foot or shoulder. Arm, C, is placed against the shoulder D; pendulum A is released when in contact with upper arm B.

To get accurate records of patients in bed it is essential that the bed be rigidly held, which can be done by putting a block under the cross bars at head or foot to lift the caster off the ground about $\frac{1}{2}$ inch and by putting a plywood board 18 by 32 inches under the patient's trunk and buttocks. If the mattress is of rubber foam or rests on box springs, this board must be fastened to the frame of the bed by suitable rubber-jawed clamps. Vibrations due to people walking in the building or to passing trucks may be troublesome in buildings with wooden beams and floors.

Standardization. When records are made from the head, standardization is effected by recording the effect of blows on the foot produced by a pendulum moving through a constant arc. When records are made from the legs, the blow is delivered to the right shoulder close to the neck. We use a 220 Gm. padded lead weight on an arm 12 cm. long, the length of the swing being fixed by a horizontal rod which touches the shoulder and is just beneath the arc of the pendulum and another which fixes the height to which the pendulum can be raised on the opposite side. (Fig. 5.) A 200,000 dyne blow

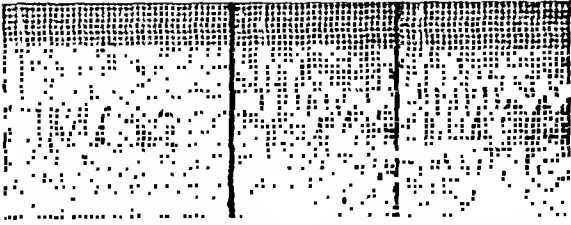


FIG. 6. Sphygmographic trace (lower) and photoelectric trace recorded from cadaver when a blow of 200,000 dynes was applied to the sole of the foot. Note progressive decrease in large oscillations, and the fine oscillations when no damping is used in the sphygmographic system. The photoelectric cell was used at the shin, but its peaks follow the sphygmographic one because of delay in the amplifier used in this original method. No amplifier is needed with the 890 cell.

gives a deflection of 8 to 10 mm. on subjects weighing 70 Kg. When using the direct writer the amplifier can be adjusted to give this deflection on each subject. In practice we rarely use this except when following change in amplitude under therapy, and with the string galvanometer merely record a series of blows so that any variations in the recording system will be evident on the records. The inherent frequency of the body is also evident from the after-waves. *

COMMENT

When the foot or shoulder of a cadaver on a table is tapped, the whole body is displaced, sliding on the panniculus and returning by oscillations to the initial position. (Fig. 6.) Each after wave is 50 to 70 per cent as high as the preceding opposite wave, and the frequency depends on the weight of the cadaver, thickness of fat pads, tissue turgor and elasticity, etc. During life the recumbent body is displaced by recoil from acceleration of the viscera and blood, or from their deceleration. Displacement is resisted and after-oscillations are set up by the panniculus since every displacement stretches pannicular fibers.

Actual motion is a resultant of displacing and restoring forces, with after-waves sometimes in phase and at others out of phase with subsequent displacing forces. The actual height of the waves set in motion by systole is dependent on velocity of cardiac ejection as much as on its volume, and except for the initial (presumably auricular) H wave, the height of each subsequent wave may, by chance, be augmented or dimin-

ished by 60 per cent of the preceding wave, depending on the inherent frequency of the body. For this reason the stroke volume calculated from these waves varies from the true value in many normal subjects. At best one can conclude that large I and J waves indicate high velocity and probably large volumes of systolic ejection, small ones low velocity and probably small volumes of ejection.

If the body could be suspended in space, without friction or periodicity of the system, a true ballistic record free of restoring forces would be inscribed and the body would move away with increasing velocity. In practice the body must rest on a surface and in the past all recording has been done from the table on which it rests. Since the table is rigidly held, the body continues to move and energy is converted to heat in the panniculus. If the table has a frequency of over 10 per second, the curves inscribed are almost identical with those inscribed from the head or legs directly. Physiologically, there is no more reason for recording the motion of the body through the table than for recording cardiac action currents from a bath tub. In practice, direct recording is much more useful. As the physiologists have pointed out, the ballistocardiograph is of value chiefly for clinical purposes and the urgent problem is to determine the significance of altered patterns "in relation to disease and prognosis."^{5,12}

CLINICAL SIGNIFICANCE OF ALTERED BALLISTOCARDIOGRAPHIC PATTERNS

In our own experience, patients with high cardiac output, even with heart failure, often have large I-J waves; those with low output or normal output may have very small waves, especially during expiration, if they are in failure, or even if they have angina of effort without congestive failure. Men under thirty-five who have recovered from myocardial infarction may show normal curves but many older men have bizarre tracings as the first objective sign of coronary disease. Starr noted that this may precede subjective or objective evidence of heart

disease.⁹ In coarctation without failure the K wave is abruptly cut off at or above the base line.^{2,5,6} After severe hemorrhage H waves are high; K waves disappear. In acute myocardial infarction low amplitude bizarre complexes repeatedly have preceded any change in the limb leads of the ECG, and in a few instances preceded the change in precordial leads.

Of particular interest to us have been the waves in diastole. Large L waves have been encountered in acute rheumatic carditis in children and adults; in normal children L waves tend to be more evident than in adults. In rheumatic carditis with mitral valve disease the L wave may be larger than J. Deep K waves occur in hypertension, with notched J waves and late K (or in reality, M) waves as failure sets in. There may be deep M waves with protodiastolic gallop, and a deep wave may precede the H wave in cases of presystolic gallop. The footward diastolic waves, in amplitude and steepness of contour, may exceed any wave due to ventricular ejection and aortic flow. Presumably they are due to deceleration of blood returning to the ventricles. The failing heart fills faster than it empties. As a rule gallop sounds occur with the deep diastolic waves but the waves may be evident before gallop is noted or persist after it has become inaudible as a result of therapy.

It seems probable that the decrease in K waves in shock is due to splanchnic and renal vasoconstriction and vasoconstriction in the skin and muscles of the legs. It may well provide anesthetists and surgeons with the first clue to the body's reaction to decreased venous return, and thus permit them to follow the onset and recovery from shock.

The ballistocardiogram gives information of a character so unlike that of the electrocardiogram and so useful to the clinician as evidence of altered circulatory conditions that it deserves wide study and application. This is now available to all who have electrocardiographic equipment, with little additional apparatus. While synchronous electrocardiograms or sound tracings are

needed to identify bizarre waves, they are not needed to distinguish normal from abnormal records.

SUMMARY

1. The motion of the body recorded by a sphygmograph applied to the head, by a photocell partly shaded by a ruler across the shins, or by a coil in a magnetic field, provides a satisfactory ballistocardiogram.

2. The records require little additional equipment for those who have portable electrocardiographs. They can be made in the ward, office, operating room or at home.

3. The records are particularly useful in angina, myocardial infarction and in shock.

REFERENCES

1. STARR, I., RAWSON, A. J., SCHROEDER, H. A. and JOSEPH, H. R. Studies on the estimation of cardiac output in man and of abnormalities in cardiac function from the heart's recoil and the blood's impacts; the ballistocardiogram. *Am. J. Physiol.*, 127: 1, 1939.
2. NICKERSON, J. L. Some observations on the ballistocardiogram with special reference to the H-K waves. *J. Clin. Investigation*, 28: 2, 1949.
3. NICKERSON, J. L. and CURTIS, H. J. The design of the ballistocardiograph. *Am. J. Physiol.*, 142: 1, 1944.
4. NICKERSON, J. L. The low frequency critically damped ballistocardiograph. *Federation Proc.*, 4: 201, 1945.
5. HAMILTON, W. F., DOW, P. and RENNINGTON, J. W. Relationship between cardiac ejection curves and ballistocardiographic forces. *Am. J. Physiol.*, 144: 557-570, 1945.
6. BROWN, H. R., HOFFMAN, M. J. and DE LALLA, V., JR. Ballistocardiogram in coarctation of the aorta. *New England J. Med.*, 240: 775-778, 1949.
7. BROWN, H. R., JR. and DE LALLA, V., JR. Deep J-K stroke associated with hypertension. (Unpublished data.)
8. STARR, I. and SCHROEDER, H. A. Ballistocardiogram. II. Normal standards, abnormalities commonly found in diseases of the heart and circulation and their significance. *J. Clin. Investigation*, 19: 437-450, 1940.
9. STARR, I. The Ballistocardiograph—An Instrument for Clinical Research and in Routine Clinical Diagnosis. The Harvey Lectures, 194-219, 1946-47.
10. BROWN, H. R., JR. and PEARSON, R. New electronic method for simultaneous recording of ballistocardiograph and electrocardiograph. *Am. Heart J.*, 35: 756-762, 1948.
11. STARR, I. Further clinical studies with the ballistocardiograph; on abnormal form, on digitalis action, in thyroid disease, and in coronary heart disease. *Tr. A. Am. Physicians*, 49: 180, 1946.
12. TANNER, J. M. The construction of normal standards for cardiac output in man. *J. Clin. Investigation*, 28: 567, 1949.

Effects of Clockwise Rotation of the Heart on the Electrocardiogram*

EMANUEL GOLDBERGER, M.D.

New York, New York

IT has been pointed out by the author¹⁻³ and by others⁴ that the position of the heart is not fixed within the thoracic cage, and that rotation of the heart can take place around one or more of the following three axes: (1) rotation of the heart around its anteroposterior axis; when this happens, the heart becomes vertical or

horizontal; (2) rotation of the heart around its long axis; clockwise rotation causes the right ventricle to face more of the anterior surface of the chest wall and the left ventricle rotates to the left; counterclockwise rotation causes the left ventricle to face more of the anterior chest wall, and the right ventricle rotates to the right; (3) rotation of the apex of the heart around its transverse axis; the apex is either rotated forward or backward.

In this paper the effects of clockwise rotation of the heart in both the precordial leads and the extremity leads will be described for both normal tracings and tracings showing signs of right or left ventricular hypertrophy. The cases illustrated were selected at random from our files.

GENERAL REMARKS

In order to correlate the electrocardiographic patterns that appear in the standard leads, augmented unipolar extremity leads, and multiple precordial leads, the following review is of value:¹⁻³

1. A unipolar lead that overlies or faces the epicardial surface of the left ventricle shows a qR pattern. (Fig. 1, Lead v_5 .)

2. A unipolar lead that overlies or faces the epicardial surface of the right ventricle shows an rS or an RS pattern. T is usually upward but may be downward. (Fig. 1, Leads v_1 - v_4 .)

3. A unipolar lead that faces the right ventricular cavity shows an rS pattern and a downward T (Fig. 1, Lead 2R_{ics}.)

4. A unipolar lead that faces the left

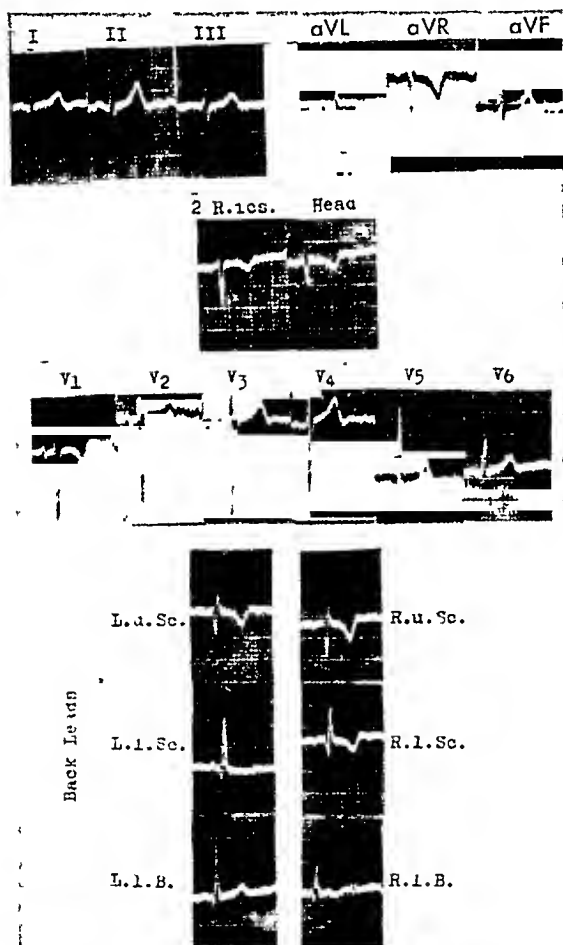


FIG. 1. Multiple unipolar leads from a normal person

* From the Medical Division, Montefiore Hospital, New York, and the Electrocardiographic Department, Lincoln Hospital, New York, N. Y.

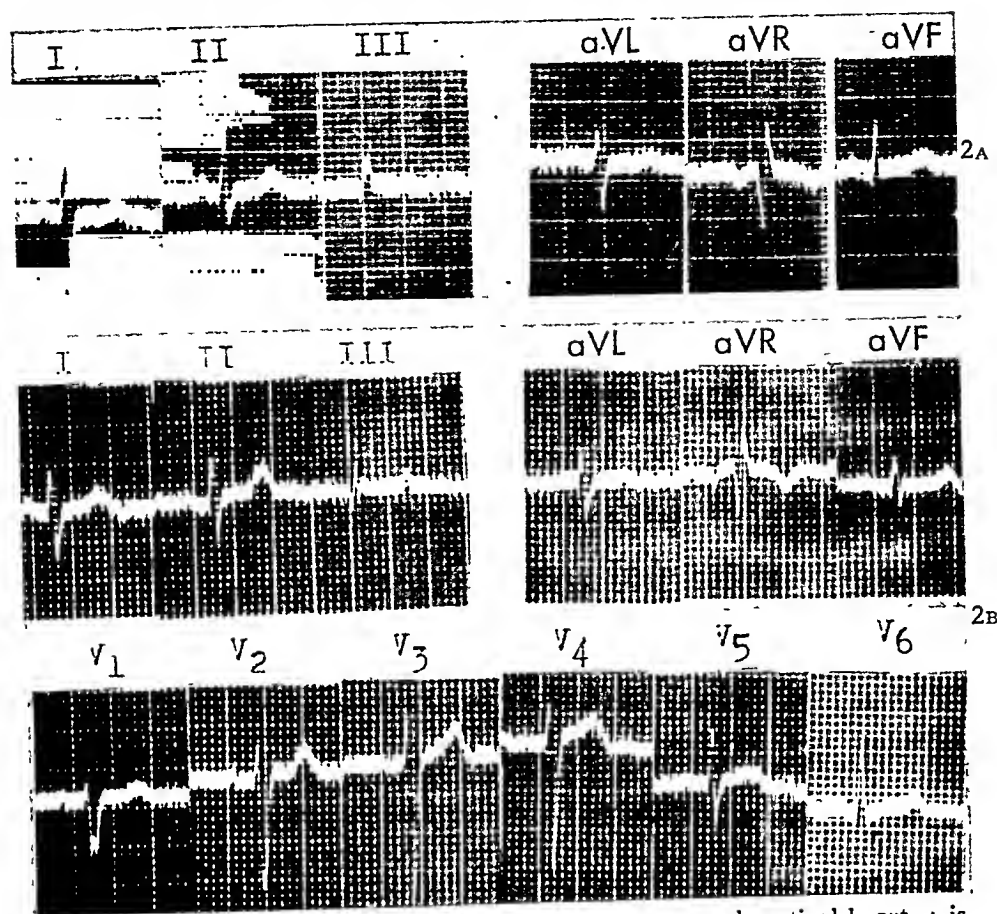


FIG. 2. The effect of marked clockwise rotation on a normal vertical heart. A is a woman, aged twenty years; B is a man, aged twenty-nine years.

ventricular cavity shows a QS deflection and a downward T. (Fig. 1, Lead Head.)

5. A unipolar lead that faces the back of the heart shows a QR (or a Qr or a qR) pattern and a downward T. (Fig. 1, Leads L.u.Sc., R.u.Sc., R.l.Sc.)

6. Although each standard lead represents a combination of potentials from two extremities, the following general relations between standard leads and unipolar extremity leads usually hold:

Lead I resembles Lead aVL or the reverse of Lead aVR.

Lead II resembles Lead aVF or the reverse of Lead aVR.

Lead III resembles Lead aVF or the reverse of Lead aVL.

7. When the heart is vertical, Lead aVL shows a QS, an rS or RS pattern. When the heart is horizontal, Lead aVL shows a qR or a QR pattern.

EFFECT OF MARKED CLOCKWISE ROTATION ON A VERTICAL HEART

When marked clockwise rotation of a vertical heart occurs, precordial Leads v_1

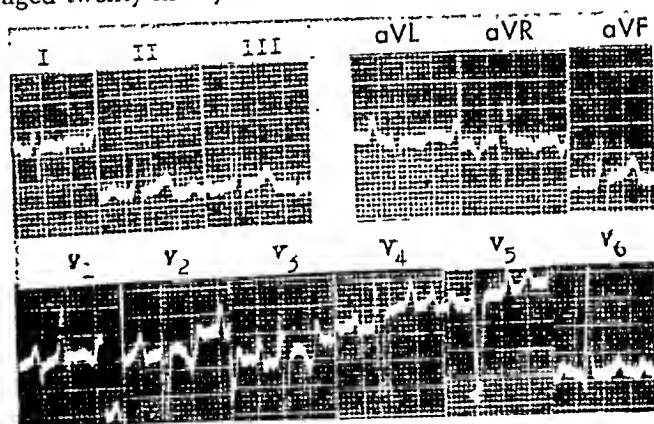


FIG. 3. The effect of clockwise rotation on a vertical hypertrophied heart.

through v_5 or v_6 may face the epicardial surface of the right ventricle and show rS and RS patterns. (Fig. 2.) Lead aVL shows an rS or RS pattern because it faces either the cavity of the right ventricle or the epicardial surface of the right ventricle as a result of the clockwise rotation. Lead aVR shows a QR type of pattern because it faces the back of the heart as a result of the marked clockwise rotation.

Figures 2A and B show such tracings in normal vertical hearts with marked clockwise rotation. Figure 2B also shows an addi-

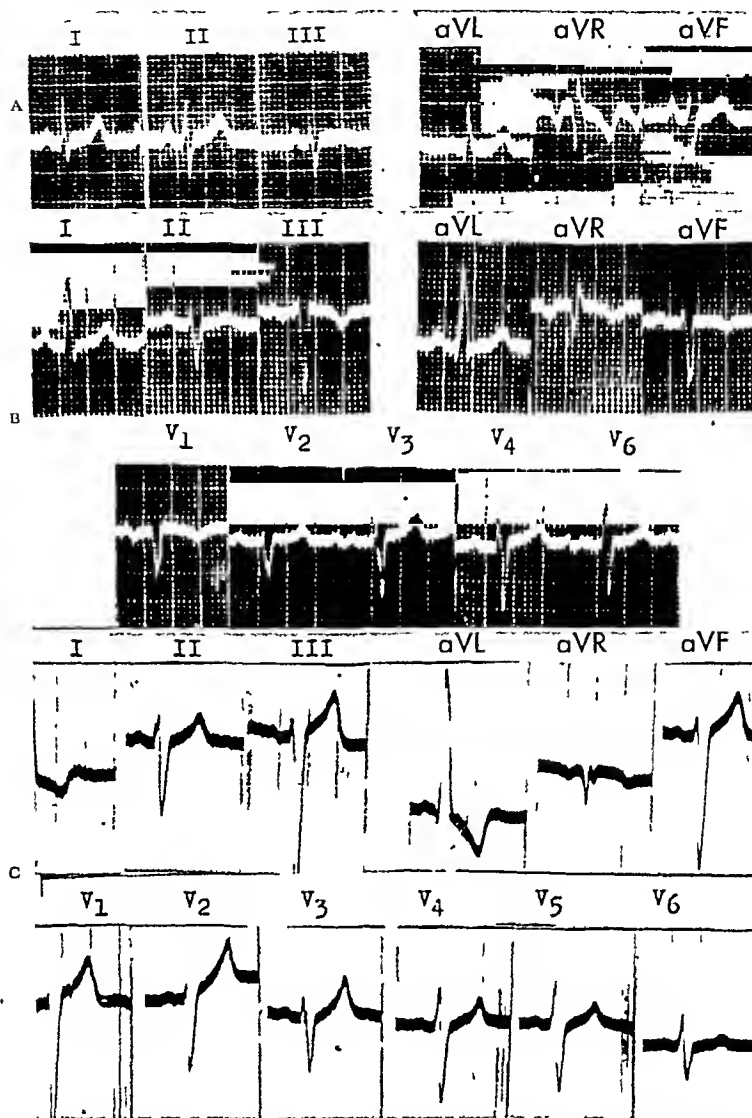


FIG. 4. A and B, the effect of clockwise rotation on normal and hypertrophied hearts with hypertensive cardiovascular disease; C, a man with hypertensive cardiovascular disease.

tional type of rotation. Ordinarily when the heart is vertical, Lead aVF faces the epicardial surface of the left ventricle and shows a qR pattern. However, if backward rotation of the apex occurs, Lead aVF faces the epicardial surface of the right ventricle and shows an rS or RS pattern as appears in Figure 2B.

Figure 3 shows the effect of marked clockwise rotation of a vertical heart in a patient who had extensive right ventricular hypertrophy. It is the tracing of a twelve year old boy who died of rheumatic heart disease. At autopsy aortic and mitral stenosis were

found and there was marked hypertrophy of both the right and left ventricles.

Lead v_1 shows a tall R and a downward T due to right ventricular hypertrophy, and the P is large and wide due to auricular hypertrophy. However, Leads v_{2-5} show RS patterns which indicate that these leads are also facing the epicardial surface of the right ventricle. Therefore, marked clockwise rotation is also present. Lead aVR shows a QR and a downward T, further indicating that marked clockwise rotation is present. Lead aVL shows an rS indicating that the heart is vertical, and Lead aVF

shows an RS instead of a qR indicating that backward rotation of the apex is present.

EFFECT OF MARKED CLOCKWISE ROTATION ON A HORIZONTAL HEART

When marked clockwise rotation of a horizontal heart occurs, all six precordial leads may show rS and RS patterns just as occurs in a vertical heart so rotated, and Lead aVR develops a QR and a downward T. However, because the heart is horizontal, Lead aVL continues to show a qR pattern. Figure 4A shows this in a normal tracing. Figures 4B and C show this in patients with left ventricular hypertrophy. In Figure 4B lead aVL shows not only a qRS pattern but R is more than 13 mm. tall. This is high voltage and indicates left ventricular hypertrophy.³ In Figure 4C Lead aVL shows not only high voltage but the depressed RS-T and downward T indicate left ventricular strain.

EFFECT OF EXTREME CLOCKWISE ROTATION ON A VERTICAL OR HORIZONTAL HEART

When clockwise rotation is extreme, the back of the heart can actually face the anterior surface of the right chest.¹ In such a case Lead v_1 and even Lead v_2 may show the pattern of the back of the heart, namely, a QR or a qR and a downward T. Figure 5 shows such a tracing, that of a patient with cor pulmonale. Precordial Leads v_{2-6} in this case show normal RS patterns.

When such extreme clockwise rotation is present, Lead aVR not only shows a QR type of pattern, but the R becomes tall with respect to the q. Although this qR pattern in Lead aVR has been interpreted as a sign of right ventricular hypertrophy,⁵ actually it is merely a sign of extreme clockwise rotation and may occur in cases not only of right ventricular hypertrophy but myocardial infarction and even in normal people. Although extreme clockwise rotation with a

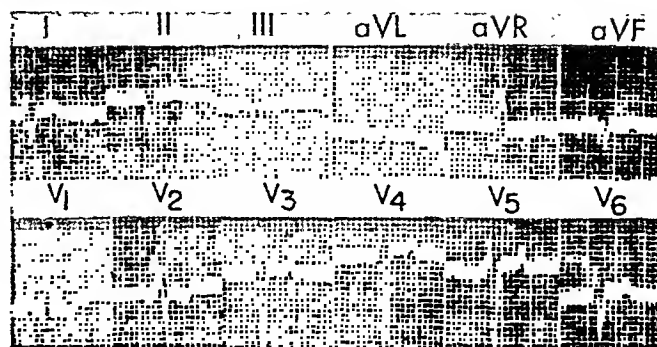


FIG. 5. The effect of extreme clockwise rotation on the heart; a patient with cor pulmonale.

qR in Lead v_1 , can theoretically occur normally, I have not seen it in any normal person.

CONCLUSIONS

1. Precordial leads as well as unipolar extremity leads and standard leads vary when clockwise rotation of the heart occurs.
2. When marked clockwise rotation of the heart occurs, precordial Leads v_1 through v_5 or v_6 may face the epicardial surface of the right ventricle and show rS and RS patterns. This may occur in a normal person with a vertical or horizontal heart, or in patients with right or left ventricular hypertrophy.
3. A further sign of marked clockwise rotation is the development of a QR, Qr or qR pattern in Lead aVR.
4. When extreme clockwise rotation is present, precordial Lead V_1 and sometimes Lead V_2 can also face the back of the heart and show a QR or qR pattern in addition to Lead aVR.

REFERENCES

1. GOLDBERGER, E. The differentiation of normal from abnormal Q waves. *Am. Heart J.*, 30: 341, 1945.
2. GOLDBERGER, E. and SCHWARTZ, S. P. The electrocardiogram in chronic pulmonary disease. *Am. Rev. Tuberc.*, 53: 34, 1946.
3. GOLDBERGER, E. Unipolar Lead Electrocardiography. 2nd ed. Philadelphia, 1949. Lea & Febiger.
4. GARDBERG, M. and ASHMAN, R. The QRS complex of the electrocardiogram. *Arch. Int. Med.*, 72: 210, 1943.
5. MYERS, G. B., KLEIN, H. A. and STOFER, B. E. The electrocardiographic diagnosis of right ventricular hypertrophy. *Am. Heart J.*, 35: 1, 1948.

Electrocardiographic Evaluation of Boeck's Sarcoid and Advanced Pulmonary Tuberculosis*

Special Reference to Interpretation of the Multiple Unipolar Leads

SAFETY R. FIRST, M.D.

Tulsa, Oklahoma

INTERPRETATION of multiple unipolar leads recorded in patients with pulmonary manifestations of Boeck's sarcoid revealed the frequent occurrence of left ventricular hypertrophy, an electrocardiographic finding which may prove to be of added value in the differentiation of sarcoidosis and tuberculosis. Sarcoidosis is a systemic disease which may involve the myocardium and account for electrocardiographic irregularities¹⁻⁴ while tuberculosis rarely involves the myocardium directly and electrocardiographic abnormalities, when present, are of different form than those observed in sarcoid. The pulmonary roentgenographic changes of sarcoidosis and tuberculosis frequently resemble each other and in many cases offer a diagnostic problem of some magnitude.

METHOD AND MATERIAL

Serial teleoroentgenograms and electrocardiograms in seven cases of Boeck's sarcoid and twenty cases of far advanced pulmonary tuberculosis were compared. The electrocardiograms were recorded by using a modified central terminal⁵ and included leads aV_L, aV_F, V₁, V₂, V₃, V₄, V₅ and V₆, in addition to limb leads I, II and III. The positions explored were those specified by the Committee of the American Heart Association for the Standardization of Precordial Leads.⁶

RESULTS

Of the seven patients with Boeck's sarcoid six gave electrocardiographic findings which were interpreted as definite evidence of left ventricular hypertrophy. One had a normal electrocardiogram. Teleoroentgenograms of five of these subjects revealed diffuse areas of infiltration scattered throughout both lung fields. One revealed a nodular enlargement of the mediastinum. A positive diagnosis was established in each case by microscopic examination of lymph node biopsies after exhaustive studies failed to show evidence of acid-fast organisms.

The electrocardiograms of twenty patients with far advanced pulmonary tuberculosis showed the following:

No. of Cases	Diagnosis
3	Incomplete right bundle-branch block
3	Pericarditis
2	Right ventricular hypertrophy
1	Moderately recent anteroseptal infarction
11	Normal

Teleoroentgenograms showed bilateral disease with cavitation in most instances and the sputum contained acid-fast organisms in each case.

ELECTROCARDIOGRAMS ILLUSTRATING CHANGES

Two months after the diagnosis of Boeck's sarcoid was made in a colored male, aged twenty-three, the electrocardiogram in Fig-

* From the Department of Internal Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

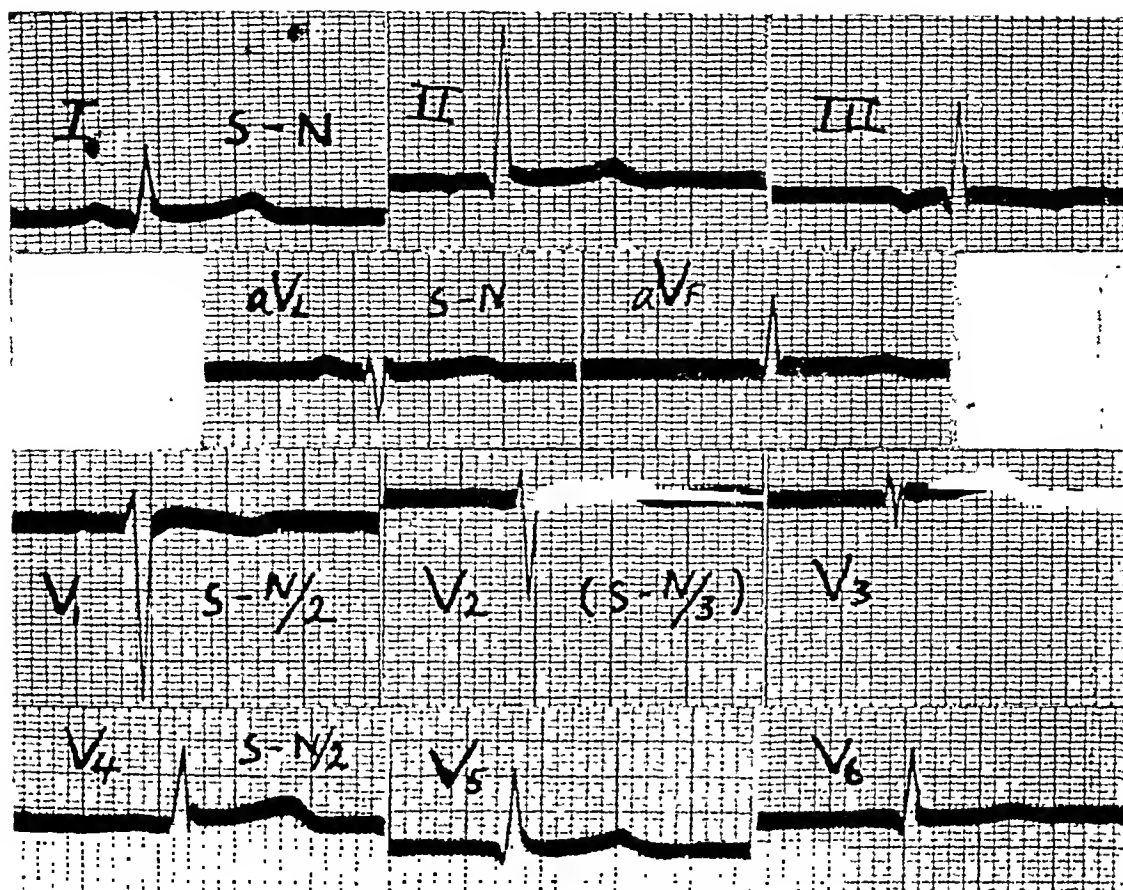


FIG. 1. Left ventricular hypertrophy.

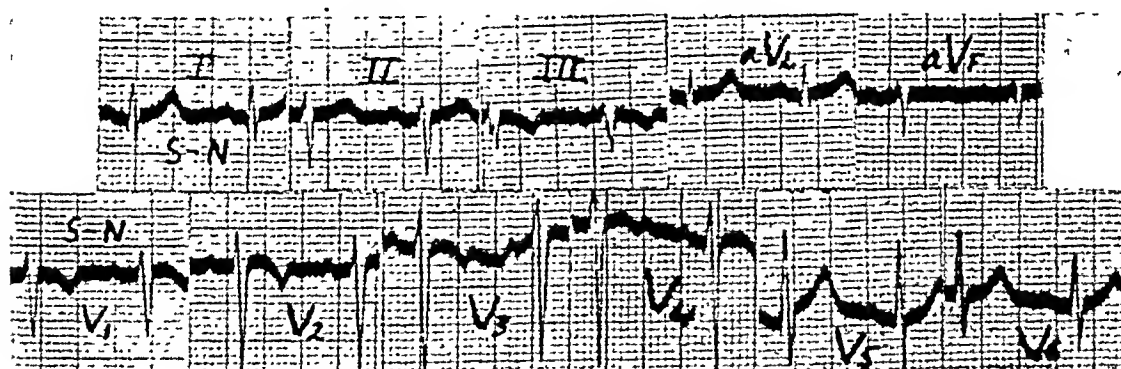


FIG. 2. Pericarditis.

ure 1 was recorded. The patient presented no subjective or objective clinical findings when a routine chest roentgenogram first indicated disease. Repeated sputum and gastric studies were negative for acid-fast organisms. The blood pressure was 120/80. Leads V_1 and V_2 which represent potential variations from the free surface of the right ventricle were recorded as one-half and one-third the normal sensitivity, respectively, and show a prominent S. Transition occurs at V_3 , following which there is a prominent R at V_5 and V_6 representing the potential variations of the left ventricle. The changes are diagnostic of left ventricular

hypertrophy; the heart is in the vertical position and the mean electrical axis of QRS (A_{QRS}) is normal. Six of the seven patients with Boeck's sarcoid presented similar changes.

The electrocardiogram reproduced in Figure 2 was recorded in a white man, aged twenty-four. The initial diagnosis of pulmonary tuberculosis was established eighteen months earlier and marked progression followed. The T wave is positively spiked in lead I and inverted in lead III. The RS-T segment is arched upward and T shows a late inversion in V_1 , V_2 , V_3 and V_4 . Transition is not complete at V_6 . The changes are

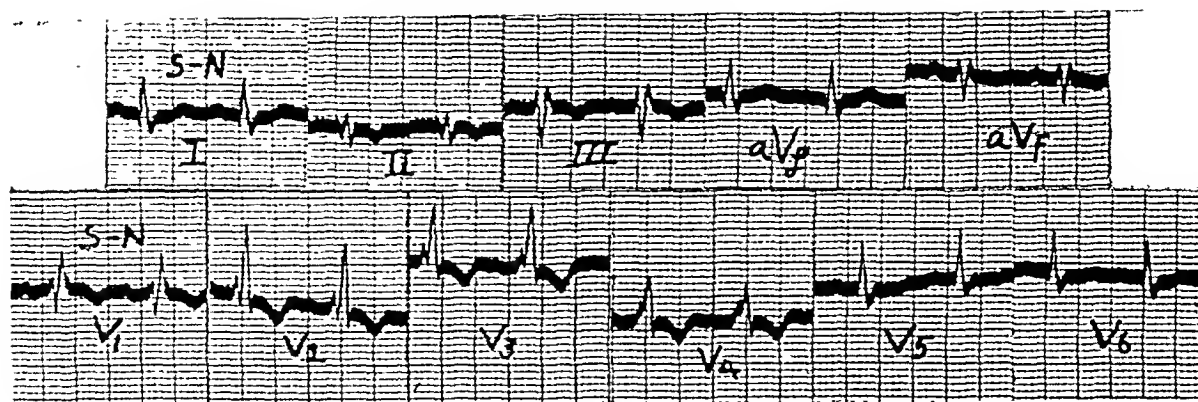


FIG. 3. Right bundle branch block.

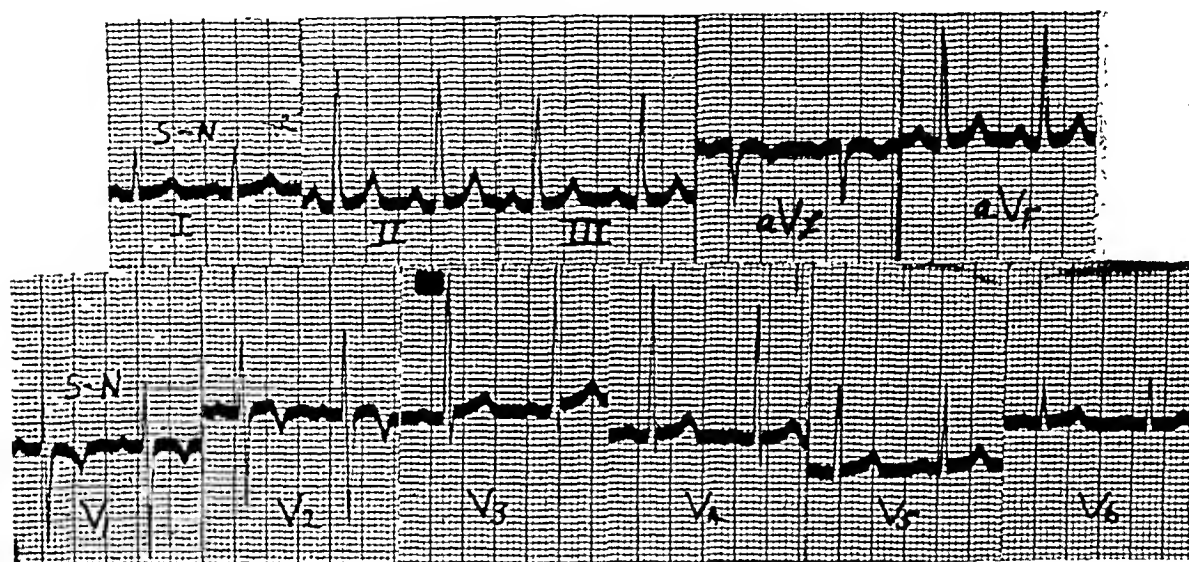


FIG. 4. Right ventricular hypertrophy.

compatible with chronic, low grade pericarditis; the heart is in the horizontal position and there is a counterclockwise rotation of A_{QRS} (left axis deviation).

The electrocardiogram which is reproduced in Figure 3 was recorded in a white man, aged thirty, in whom a diagnosis of far advanced pulmonary tuberculosis had been established by positive sputum and gastric washings and chest roentgenographic changes. The QRS interval is 0.12 seconds and the S is broad in lead I. R and R' deflections are present in leads aV_F , V_1 , V_2 and V_3 . Transition occurs between V_4 and V_5 ; V_5 and V_6 are contributions to the precordium from the left ventricular surface and show a broad S. The heart is in the horizontal position and there is a counterclockwise rotation of A_{QRS} . When the right

branch of the His bundle is blocked, accession of the interventricular septum from the left branch produces an initial positive potential at the surface of the right ventricle whereas late accession of the free wall of the right ventricle produces a second positive variation at this surface late in the QRS interval. These two positive variations undoubtedly exert a dominant effect in the formation of R and R' in leads aV_F , V_1 , V_2 and V_3 .⁷⁻⁹

The electrocardiogram (Fig. 4) was recorded in a white man, aged twenty, who had shown a slowly progressive disease for two years. Sputum and gastric washings were positive for acid-fast organisms and the chest roentgenogram revealed exudative disease with cavitation. R is prominent at V_1 and V_2 where T is rounded and shows a

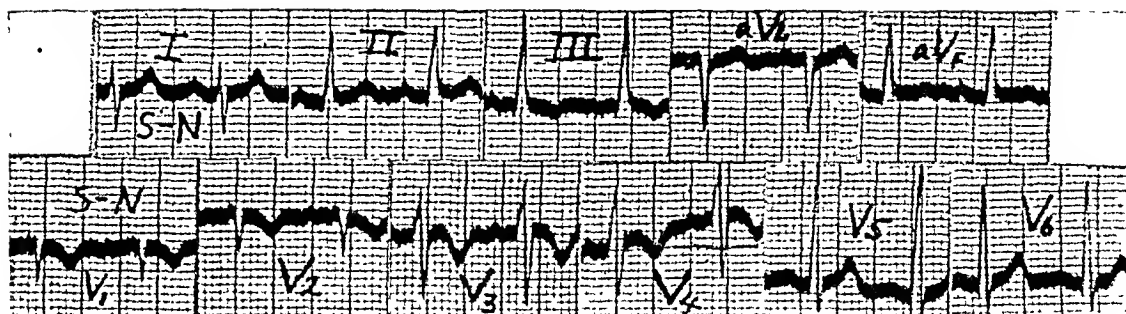


FIG. 5. Anteroseptal infarction.

terminal negative deflection. Transition occurs between V_2 and V_3 . V_3 , V_4 , V_5 and V_6 are the potential variations transmitted to the precordium from the surface of the left ventricle. These changes suggest right ventricular hypertrophy, the heart in the vertical position and a tendency toward clockwise rotation of A_{QRS} .

The electrocardiogram (Fig. 5) was recorded in a white male, aged thirty-four, one year following the initial diagnosis of pulmonary tuberculosis and two weeks following an attack of precordial pain which radiated to his left shoulder and was accompanied by dyspnea and orthopnea. Sputum and gastric washings were positive for acid-fast bacilli and the teleroentgenogram revealed far advanced pulmonary disease. R is minute in leads aV_L , V_1 and V_2 and is low with a slurred upstroke in V_3 . T is inverted in leads V_1 , V_2 , V_3 and V_4 . In view of the history and these changes a diagnosis of moderately recent anteroseptal infarction appears justified; the heart is in the vertical position and there is clockwise rotation of A_{QRS} . Characteristically, when precordial lead changes are confined to V_1 , V_2 and V_3 , little or no change is present in the limb leads.

COMMENTS

Sarcoidosis is considered to be a systemic disease in which no organ is exempt from possible involvement. Schaumann, in his initial publication,¹⁰ described sarcoid involvement of the myocardium in post-mortem material. His observation has been confirmed on numerous occasions and various electrocardiographic conduction irregularities have been reported.¹⁻⁴ Unipolar

chest leads were not employed in these observations, however, and consequently the repeated finding of left ventricular hypertrophy in these cases is of interest. Why the left ventricle is selectively involved is unexplained. Perhaps sarcoidosis, like rheumatic fever, has a tendency to localize in the heart with an intensity which is proportional to the work done.

As a general rule pulmonary tuberculosis is unaccompanied by changes in the electrocardiogram unless there is involvement of the pericardium. In far advanced pulmonary disease secondary myocardial changes may occur and account for secondary alterations in the heart's electrical field. It was for this reason that patients with far advanced pulmonary tuberculosis were selected for this study. Of twenty patients only five presented abnormal curves which could be attributed to pulmonary disease.

SUMMARY

1. Left ventricular hypertrophy produced by Boeck's sarcoid can be detected in the precordial electrocardiogram.
2. A few patients with sarcoidosis presented electrocardiographic changes which differed from those encountered in a group of twenty patients with far advanced pulmonary tuberculosis. These differences, if equally consistent in larger groups, might prove helpful diagnostic leads.

Acknowledgment: An expression of thanks is extended to Dr. Robert H. Bayley for helpful criticism in the preparation of this manuscript.

REFERENCES

1. LONGCOPE, W. T. and FISHER, A. M. The effect of Schaumann's disease upon the heart and its mechanism. *Acta med. Scandinav.*, 108: 529, 1941.

2. LONGCOPE, W. T. and FISHER, A. M. Involvement of the heart in sarcoidosis or Besnier-Boeck-Schaumann's disease. *J. Mt. Sinai Hosp.*, 8: 784, 1942.
3. JOHNSON, J. B. and JASON, R. S. Sarcoidosis of the heart—report of a case and review of the literature. *Am. Heart J.*, 27: 246, 1941.
4. SALVESEN, H. A. The sarcoid of Boeck, a disease of importance to internal medicine. *Acta med. Scandinav.*, 86: 127, 1935.
5. GOLDBERGER, EMANUEL. A simple, indifferent, electrocardiographic electrode of zero potential and a technique of obtaining augmented, unipolar, extremity leads. *Am. Heart J.*, 23: 483, 1942.
6. Supplementary Report by the Committee of the American Heart Association for the Standardization of Precordial Leads. *Am. Heart J.*, 15: 235, 1938.
7. WILSON, F. N., JOHNSTON, F. D. and BARKER, P. S. Electrocardiograms of an unusual type in right bundle-branch block. *Am. Heart J.*, 9: 472, 1934.
8. WILSON, F. N., JOHNSTON, F. D., ROSENBAUM, F. F., ERLANGER, H., KOSSMANN, C. E., HECHT, H., CORTIM, N., DEOLIVEIRA, R. M., SCARSI, R. and BARKER, P. S. The precordial electrocardiogram. *Am. Heart J.*, 27: 19, 1944.
9. WILSON, F. N., JOHNSTON, F. D., ROSENBAUM, F. F. and BARKER, P. S. On Einthoven's triangle, the theory of unipolar electrocardiographic leads, and the interpretation of the precordial electrocardiogram. *Am. Heart J.*, 32: 277, 1946.
10. SCHAUMANN, J. Lymphogranulomatosis benigna in the light of prolonged clinical observations and autopsy findings. *Brit. J. Dermat.*, 48: 399, 1936.

Hemiplegia Attending Acute Myocardial Infarction*

WILLIAM BENNETT BEAN, M.D., GERALD W. FLAMM, M.D. and ALBERT SAPADIN, M.D.

Iowa City, Iowa

Brooklyn, New York

Cincinnati, Ohio

OCCASIONAL reorientations in medical thought are useful goads against the dogma which too readily encases our ideas in fixed mental habits. It is usually taken for granted that such an episode as hemiplegia occurring at the time of acute myocardial infarction or shortly after is embolic in origin, the embolus in question coming from a ventricular mural thrombus. Some years ago, in surveying a large series of cases of myocardial infarction proved at autopsy, it was noted that the majority of cases of hemiplegia which followed infarction of the heart were associated with cerebral arteriosclerosis and local thrombosis or even hemorrhage rather than with emboli.¹ Still later, in association with Read² one of us (W. B. B.) reported several instances of hemiplegia as the presenting symptom of acute myocardial infarction. There was advanced arterial disease of the brain but no acute lesion of the cerebral arteries to account for the major symptoms. It was suggested that the reduction in blood flow, affecting particularly the cerebral foci with the most severely diseased arteries, determined the clinical picture. This striking masquerade of coronary thrombosis with a neurologic debut has not aroused the interest of cardiologists or caught the attention of internists though it is better known to some neurologists.³ It is, however, sufficiently important that its recognition not be confined to those isolating themselves in any medical specialty.

It is impossible to prove the nature of this type of case except by postmortem study of heart and brain. It is possible, indeed probable, that less serious cases of like

nature occur. In an attempt to discover them clinically we have taken electrocardiograms in many patients admitted to the hospital with hemiplegia. In several patients not included in this study the medical history revealed that hemiplegia had ensued shortly after cardiac infarction. In only one such case was the diagnosis proved. The others either recovered or died and no autopsy was performed.

At times there is difficulty in assigning an exact time to the onset of an acute myocardial infarct.¹ In the instances we are reporting the lesion in the heart gave testimony of an age in keeping with the known time of collapse or pain which we have used as the clinical landmark indicating the acute onset of myocardial infarction.⁴ The present study casts no light on the possibility that hemiplegia from cerebral hemorrhage or thrombosis, and hyperactivity or convulsions associated with it might themselves precipitate coronary thrombosis or myocardial infarction. The absence of the acute lesion, cerebral thrombus or hemorrhage in our cases indicates that the central nervous system was not primarily concerned but manifestations referable to it were concomitants or early sequelae of the acute myocardial infarction.

We have reviewed the protocols of all autopsies done in the Department of Pathology for the years 1941 through 1946 to look for cases in which hemiplegia was precipitated by acute myocardial infarction. We set up as criteria for selection the presence of (1) a gross recent infarct of the heart measuring at least 3 by 3 cm. and (2) focal neurologic signs suggesting cerebral

* From the Departments of Medicine and Pathology of the University of Cincinnati and the Cincinnati General Hospital, Cincinnati, Ohio.

hemorrhage, thrombosis or embolus but the (3) absence of any gross evidence of an acute vascular lesion of the cerebral vessels. The six cases discussed in this report were found. Pronounced arteriosclerosis of the larger cerebral vessels was present. It has been the experience of some pathologists that emboli and thrombi are overlooked unless special precautions are taken to find them. An injection plus dissection of the arteries supplying the brain would have given assurance that there were indeed no acute vascular lesions of larger cerebral arteries but such a procedure was not carried out. While no rigid technique was followed, emboli, thrombi or hemorrhage were sought specifically because of the clinical diagnosis of hemiplegia. It is unlikely that any lesion of major importance was missed although the possibility exists.

Some cases had to be discarded because the autopsy had not included examination of the brain. There are other examples of cardiac origin for non-embolic hemiplegia, including such different diseases as aortic stenosis, dissecting aneurysm^{5,6} and rupture of a syphilitic aneurysm; all without acute vascular lesions of major cerebral vessels but with pronounced cerebral arteriosclerosis. Clinical evidence in some instances, especially in which transient hemiplegia occurred in aortic stenosis, demonstrated a relationship between the neurologic crisis and a fall in arterial blood pressure; in other cases this mechanism was suspected but not proved. An analogy between the physiologic disturbance of this condition and the syndrome of sensitive carotid sinus may exist.

REVIEW OF THE LITERATURE

Bean and Read² in 1942 called attention to a syndrome of hemiplegia attending acute myocardial infarction with the neurologic signs and symptoms overshadowing the acute cardiac disorder. They pointed out that hemiplegia and acute infarction of the heart occurring in the same patient might be (1) independent of each other, (2) the cerebral disorder might be an

embolic sequel of dislodging a ventricular mural thrombus or (3) shock resulting from the acute cardiac disorder might be associated with cerebral ischemia, especially when arteriosclerosis of vessels in the brain was advanced, and thus produce hemiplegia. The resulting symptoms and signs were thought to have been determined by the focal pattern of vascular sclerosis in the cerebral arteries. In a review of medical papers related to this topic no proved instances of hemiplegia after myocardial infarction without embolism were found, although there were numerous observations that other acute cardiac episodes might be associated with transitory palsies and paralyzes. Since this paper there has been scant notice of the problem. Cookson⁷ emphasized fits and faints as signs of cardiac infarction and commented on the old age and poor prognosis of his patients. He believed that reflex bradycardia was more important than hypotension in the production of syncope, but disease in cerebral vessels was considered to be another factor. Race and Lisa⁸ found that 15 per cent of 100 autopsied cases of myocardial infarction had lesions of cerebral vessels. For the most part in those with central nervous system lesions the cardiac disease had not been diagnosed. There were indeed five cases in which the only acute vascular lesion was coronary thrombosis but the neurologic aspects of the signs and symptoms had indicated only hemiplegia and presumably the mechanism was the same as reported by others.² Fisher and Zukerman⁹ found three cases of cerebral hemorrhage and two of cerebral thrombosis in 108 cases of myocardial infarction but did not discuss the time relationship of the episodes or the accuracy of the clinical diagnosis.

Four mechanisms for the production of hemiplegia following acute myocardial infarction may exist. *Embolism, thrombosis and hemorrhage* have been noted fairly often, but *ischemia* most pronounced in regions whose arterial supply is reduced by arteriosclerosis may be another important factor.² There

are certain common time sequences which should suggest which of these mechanisms is responsible for hemiplegia in a given instance if the train of events is known from an accurate history, which may be difficult or impossible to learn in a patient with a stroke. If hemiplegia has its onset at the same time or shortly after the acute cardiac infarction as a syncopal or apoplectic seizure while shock is prominent, the usual mechanism is cerebral ischemia and hypoxia. When its onset is somewhat later, after the first few hours but usually within the first few days up to a week, a large cerebral vessel may have become occluded by a thrombus or cerebral hemorrhage may have occurred as a result of sustained vasoparalysis.¹⁰ Evidence has been adduced that following acute myocardial infarction there may be an abnormal tendency for blood to clot rapidly.¹¹ After the first week an embolus from a mural thrombus on the endocardial wall may lodge in the brain and suddenly cause hemiplegia. Those divisions of time are not absolute. Recurring shock may follow acute myocardial infarction and give rise to hemiplegia, or an embolus from an auricular thrombus may become detached soon after acute cardiac infarction. In general the correct clinical diagnosis can be suspected if the time relationship of hemiplegia and infarction of the heart is known.

The vasotonic and physical forces which maintain the dynamics of cerebral blood flow have been the subject of much study but many aspects of the problem are not yet clearly understood. Aring³ has given a comprehensive and critical review of the physiologic control of cerebral circulation. Extracerebral factors are recognized as most important in governing intracerebral blood flow. There are, however, relatively weak neurovascular mechanisms, and humoral factors such as CO₂, pH changes and chemical agents may affect vessel caliber and blood flow. Villaret and Cachera¹² studied the effects of emboli in the form of particulate matter introduced into the cerebral circulation, and through skull

windows were able to observe venous engorgement and hemorrhagic infarction. A clue to possible mechanisms in our own cases and the close connection between cerebral hemorrhage and thrombosis is found in Scheinker's¹⁰ observation on vasoparalysis and the ensuing vasothrombosis. He found that as a result of such varied stimuli as physical trauma, sulfonamide intoxication, carbon monoxide poisoning and arsenical encephalopathy the brain might be injured gravely. By histologic study he traced the changes from vasodilatation through vasoparesis to vasoparalysis leading to stasis, diapedesis and finally to the coalescence of many minute hemorrhages. Presumably an even earlier stage in his cases may have been vasoconstriction so intense or so sustained that the resulting hypoxia led to changes in vascular endothelium.

Since some of our autopsy material has been found to manifest similar vascular changes, we suggest that the phenomenon of hemiplegia may be initiated by a fall in arterial blood pressure associated with the early state of myocardial infarction. Cerebral arteries with enough organic obstruction to reduce the blood flow critically may determine the area or areas most severely affected. If anoxia continues long enough, alterations of the walls of small vessels may permit the escape of blood. By the coalescence of many small hemorrhages a large infarct may be formed. If, however, shock is not of sufficient duration or intensity, vascular alterations may not be demonstrable even though cerebral cell function or structure may be disordered. Indeed there is presumably a stage at which complete recovery is possible, and we have observed cases clinically in which this situation was suspected although it could not be proved.

There is little in the way of therapy which can be suggested for the cerebral disturbance. If it is realized that the neurologic changes may be reversible, however, the customary nihilistic attitude toward hemiplegia may change to a more opti-

mistic one, even though the prognosis may still be none too good with an acute cardiac infarct. Where shock associated with an acute myocardial infarct causes local or general neurologic signs apparently of primary cranial origin, the correct interpretation may be vital to the management of the patient. If it is possible to improve the function of the heart and if this is done early, the stroke may disappear rapidly and an apoplexy apparently disastrous may prove transitory. Since it is not possible to make a definitive diagnosis of this cerebral masquerade of acute cardiac infarction without anatomic proof, the most that can be expected in the diagnosis of non-fatal examples of this syndrome is a properly guided suspicion which will direct treatment toward the heart rather than the head.

The following brief case reports include all proved cases of this syndrome which have come to autopsy since our earlier report.² The pathologic findings are outlined in Table I.

CASE REPORTS

CASE I. C. V., a seventy year old white man, was admitted to the Neurology Service on February 26, 1944, having collapsed at home. He had slept after dinner and upon awakening had gone to the toilet because he felt nauseated. There he vomited. Pallor, weakness and profuse perspiration occurred and he fainted. He had complained of no pain before he lost consciousness.

Physical examination revealed the temperature to be 101°F., pulse 80, respirations 28, blood pressure 230/110. The patient was a plethoric old man, stuporous and had difficulty with respiration. He demonstrated purposeless involuntary movements and was unresponsive. He showed no signs of heart failure. The heart was enlarged and a systolic murmur was heard at the apex. There was left facial weakness, symmetrical hyperreflexia and bilateral Babinski signs.

Laboratory findings were as follows: the erythrocyte count was 4.9 m.; leukocyte count 5,800; hemoglobin 15 Gm.; blood urea nitrogen was 16 mg. per 100 cc.; urine examination was normal. Lumbar puncture revealed normal pressure, negative Pandy test, 20 red blood cells and 1 white blood cell per cu. mm. The

cerebrospinal fluid protein was 40 mg. per 100 cc.

He died eleven hours after admission following a progressive downhill course. The clinical diagnoses were cerebral hemorrhage and hypertensive cardiovascular disease.

CASE II. F. W., an eighty-two year old white man, was admitted to the Neurology Service on June 15, 1944, having collapsed at home where he was found conscious on the floor but unable to move because of a left hemiparesis. Before falling he had been dizzy.

Physical examination revealed the temperature to be 101.2°F., pulse 120, respirations 30, blood pressure 125/80. The patient was an alert, acutely ill man with left hemiparesis but no evidence of heart failure. Breath sounds were stertorous so the heart sounds were obscured. A Kernig sign was elicited; there was hyporeflexia and swallowing was difficult.

Laboratory data were as follows: erythrocytes 5.05 m.; leukocytes 16,550; hemoglobin 14.3 Gm., no urine was collected. Lumbar puncture was normal with the cerebrospinal fluid protein 22 mg. per 100 cc.; blood urea nitrogen 65 mg. per 100 cc.; blood Kahn was negative.

Fluids were aspirated and respiratory distress increased. He died two days after admission. The diagnoses were thrombosis of the right middle cerebral artery and pneumonia.

CASE III. W. B., a seventy-one year old white man with a history of anginal attacks, was admitted to the Medical Service on February 4, 1946, because of marked respiratory difficulty. One week before admission the patient had become ill, vomited, was weak and became dyspneic. There was chest pain with the attack. He became especially weak on the left side after the acute attack but the exact time when hemiplegia occurred could not be learned.

During physical examination pulse and blood pressure readings were not obtainable; respirations were 45. He was cyanotic and dyspneic and coarse rhonchi obscured the heart sounds. The left arm and leg were not moved; the patient puffed out his left cheek with respirations and no reflexes could be elicited on the left.

No blood count was taken or urinalysis performed. Postmortem cisternal puncture yielded normal cerebrospinal fluid with 5 lymphocytes per cu. mm.; blood urea nitrogen was 20 mg. per 100 cc.

He died one hour after admission. Diagnoses were acute myocardial infarction with left hemiplegia, probably due to embolus.

TABLE I

			Heart										Brain							
Age	Sex	Race	Coronary Arteries				Infarcts		Mural Thrombus				Periph- eral In- farcts	Weight (Gm.)	Arterio- sclerosis	Thrombosis or Hemorrhage	In- farct	Edema	Atro- phy	Horizontal Section
			Arterio- sclerosis	Left Anterior Descend- ing	Circum- flex	Right	Healed	Recent	Auricular		Ventricular									
									Right	Left	Right	Left								
70	M	W	2+	Patent	Patent	Patent	0	Septum and parts of left ventricle	0	0	0	0	4+ with elevated plaques	Petechiae and 1 small hemorrhage in left frontal lobe, no gross thrombus	0	0	0	Petechiae and 1 small hemorrhage in left frontal region	
82	M	W	3+	Narrow	Narrow	Narrow	Tip of apex and posterior wall of left ventricle	Surrounding old one	0	0	0	Large	1,365	3+ with elevated plaques	0	0	0	2+	Atrophy with enlarged ventricles	
71	M	W	3+ with ulcerated plaques	Narrow	Narrow	Narrow	Apex and anterior lateral wall of left ventricle	Apex, anterior wall, left ventricle and septum	0	0	0	Large	1,100	1+	Congestion and small petechiae in corona radiata, no gross thrombus	0	3+ right frontal	1+ focal	Focal atrophy, some swelling, congestion petechiae	
77	F	W	4+	Narrow	Thrombosis and marked stenosis	Thrombosis and marked plaque formation	0	Posterior left ventricle	0	0	0	0	1,320	3+ with elevated plaques	0	0	1+	0	Slight congestion of basal ganglia and brain stem	
77	M	W	3+ with plaques	Occluded	Narrow	Narrow	0	Septum and anterior, lateral and posterior wall left ventricle	0	0	0	Large	1,365	1+	0	0	1+	0	Slight swelling in parietal region	
68	F	C	4+ with a few plaques	Narrow	Narrow	Narrow	0	Anterior and inferior parts of septum and anterior wall of left ventricle	0	0	0	0	3+	0	0	1+	0	Slight swelling of white matter	

CASE IV. M. B., a seventy-seven year old white woman, was admitted to the Neurology Service on April 21, 1946, after having been found on the floor at home.

Physical examination showed: pulse 100, respirations 36, blood pressure 85/65. She was very dyspneic. Coarse rhonchi obscured the heart sounds. Both arms were flaccid but tendon reflexes were retained while the legs were moved on noxious stimulation but were areflexic. Corneal reflexes were absent.

Laboratory data were as follows: red blood cells 4.82 m.; white blood cells 4,750; hemoglobin 14 Gm. Urine showed 2+ albumin and occasional white blood cells; blood urea nitrogen 24 mg. per 100 cc. Wassermann reaction was negative. Lumbar puncture was normal with a cerebrospinal fluid protein of 43 mg. per 100 cc. An electrocardiogram was interpreted as left ventricular preponderance and probable anterior myocardial infarction.

Death occurred three hours after admission. Diagnoses before the electrocardiogram was taken were cerebral hemorrhage or thrombosis, acute pulmonary edema and possible myocardial infarction.

CASE V. G. S., a seventy-seven year old white man, was admitted to the Medical Service on March 18, 1947, after becoming delirious following a sudden collapse. His pulse was 40, respirations 14 and blood pressure 75/40. The patient had Cheyne-Stokes respirations. Both lungs were filled with coarse rhonchi and wheezes. No cardiac enlargement was detected. Heart rhythm was periodically irregular and heart sounds were distant. The right arm and leg were spastic. Reflexes were increased in the arms and absent in the legs and there was a Babinski sign on the right.

Laboratory data were as follows: red blood cells 5.27 m.; white blood cells 15,200 with 93 per cent polymorphonuclears. Urine showed 2+ albumin, occasional white blood cells and 2 to 3 red blood cells per high power field; blood urea nitrogen 60 mg. per 100 cc. An electrocardiogram showed complete A-V dissociation with idioventricular rhythm.

Therapy included sedation, plasma and fluids. Soon after admission he went into peripheral circulatory failure, became confused and developed a left hemiparesis, weakness and acute respiratory distress. He died forty-two hours after admission. The diagnoses were myocardial infarction, cerebral vascular accident and hypostatic pneumonia.

CASE VI. K. C., a sixty-eight year old colored woman, was seen in the Receiving Ward on April 18, 1947, after having collapsed on the street. She had been treated in the Outpatient Department for hypertension and heart failure of long duration. Pulse was 100, respirations 30, blood pressure 70/?. She was semicomatose and showed fine convulsive movements of the right arm, neck and face. There was an abrasion of the left temple. She did not move her left arm or leg and showed weakness of the left face. Reflexes were of no localizing value. Respirations were very labored during the dyspneic phase of her Cheyne-Stokes breathing. Basal rales and wheezes were prominent in the chest. The heart was enlarged with sinus rhythm and premature beats but no murmurs, friction rubs or gallop rhythm. Neck vein distention was notable and the liver extended 3 fingersbreadth below the right costal margin. Ankle edema was absent.

No blood count was taken. The urine showed rare white blood cells. Lumbar puncture showed initial pressure of 220 mm. of water with no change in pressure after removal of 7 cc. of fluid. There were 48 red blood cells and 7 white blood cells per cubic mm. and the cerebrospinal fluid protein was 47 mg. per 100 cc., blood urea nitrogen 21, sugar 294 per 100 cc., CO₂ 20.5 volumes per cent. Lateral skull films suggested a fracture in the region of the left lambdoidal suture. An anteroposterior chest film showed an enlarged heart.

Intravenous fluids were started and stimulants given but she died shortly after arriving at the hospital. Diagnoses were hypertensive cardiovascular disease with cardiac insufficiency, possible myocardial infarction, probable encephalomalacia in right internal capsule and possible subdural hematoma.

COMMENT

Our experience with a type of stroke which attends the early phases of acute myocardial infarction has been outlined. In this hospital it has constituted an important although relatively uncommon problem. The diagnosis is often missed because clinicians who see this type of patient are not aware that the cause of "apoplexy" can be other than thrombus, embolus or hemorrhage. It is evident from a survey of pertinent medical papers^{2,7,8} that many disturbances of cardiac function such as

paroxysmal arrhythmias, acute left ventricular failure, shock and postural hypotension may be attended by hemiplegia which may be as transitory as the provoking disturbances in the heart or may persist after the heart resumes more nearly normal function. In addition to the clear-cut entity of hemiplegia it is probable that in at least some instances confusion, coma, delirium, fainting and convulsions which may usher in, attend or follow shortly upon the acute episode of myocardial infarction, depend on the reduction in blood flow which affects the cerebral tissues according to the degree and locus of disease in the arteries supplying the brain. Reflexes may also have a part in the disturbance in cerebral blood flow but this remains a speculation. Luminal changes or spasm of sclerotic or calcified vessels could hardly reach major proportions.

In some of the brains in the present series of cases the changes found are characteristic of the vasoparalysis described by Scheinker.¹⁰ It is believed that the ensuing deterioration of brain cells is adequate to account for the continuation of hemiplegia until death. In probable instances of this kind in which hemiplegia is fleeting, recovery leaves the exact diagnosis in doubt but some of the rapidly clearing strokes may be of this nature. In the occasional instance in which transient hemiparesis is repeated in a recurring pattern the clinical picture may be explained by restricted blood flow through a diseased cerebral artery rather than vascular spasm in a "sensitized" or conditioned artery. Systemic hypoxia associated with heart failure and pulmonary congestion may aggravate an already serious condition and further the disintegration which finally causes death.

CONCLUSIONS

Clinical and morphologic data have been presented in six patients with major symptoms of acute cerebral disturbance associated with recent infarction of the heart. In all but

two a myocardial infarct was suspected clinically.

Suggestive evidence has been advanced that the pattern of local arterial disease in the brain determined the clinical signs and symptoms. A reduction of cardiac output following infarction of the heart thus may lead to the clinical masquerade of an acute cerebral vascular accident.

If the hypodynamic state is severe enough or lasts long enough, vasoparesis, vasoparalysis and coalescing small hemorrhages may occur.

The syndrome has received little attention. If properly identified and treated, there is some chance that one form of "stroke" will warrant a more optimistic outlook.

REFERENCES

1. BEAN, W. B. Infarction of the heart. II. Symptomatology of acute attack. *Ann. Int. Med.*, 11: 2086, 1938.
2. BEAN, W. B. and READ, C. T. Central nervous system manifestations in acute myocardial infarction. *Am. Heart J.*, 23: 362, 1942.
3. ARING, C. D. Vascular diseases of the nervous system. *Brain*, 68: 28, 1945.
4. MALLORY, G. K., WHITE, P. D. and SALCEDO-SALGAR, J. The speed of healing of myocardial infarction. *Am. Heart J.*, 18: 647, 1939.
5. WOOD, F. L., PENDERGRASS, E. P. and OSTRUM, H. W. Dissecting aneurysm of the aorta with special reference to its roentgenographic features. *Am. J. Roentgenol.*, 28: 437, 1932.
6. BAER, S. and GOLDBURGH, H. L. The varied clinical syndromes produced by dissecting aneurysm. *Am. Heart J.*, 35: 198, 1948.
7. COOKSON, H. Fainting and fits in cardiac infarction. *Brit. Heart J.*, 4: 163, 1942.
8. RACE, G. A. and LISA, J. R. Combined acute vascular lesions of brain and heart, a clinico-pathologic study of 15 cases. *Am. J. M. Sc.*, 210: 732, 1945.
9. FISHER, R. L. and ZUKERMAN, M. Coronary thrombosis. *J. A. M. A.*, 131: 385, 1946.
10. SCHEINKER, I. M. Vasoparalysis of the central nervous system, a characteristic vascular syndrome significance in the pathology of the nervous system. *Arch. Neurol. & Psychiat.*, 52: 43, 1944.
11. OGURA, J. H., FETTER, N. R., BLANKENHORN, M. A. and GLUECK, H. I. Changes in blood coagulation following coronary thrombosis measured by the heparin retarded clotting test (Waugh and Rudick test). *J. Clin. Investigation*, 25: 586, 1946.
12. VILLARET, M. and CACHERA, R. Les Embolies Cerebrales. P. 133. Paris, 1939. Masson et Cie.

The Role of Allergy in the Pathogenesis of Rheumatic Fever*

EDWARD E. FISCHER, M.D.

New York, New York

AFTER a half century of clinical observation and investigation the group A hemolytic streptococcus has been well established as the causative agent of the great majority of cases of rheumatic fever, a preceding streptococcus infection having been documented by numerous methods. However, the mechanism by which streptococcal infection brings about the disease state, rheumatic fever, is still obscure. This discussion will be concerned with one of the suggested etiologic mechanisms, that pertaining to bacterial allergy. Many of the factors which have been thought to participate in the genesis of rheumatic disease are considered in their relationships to the biochemical, immunologic and pathologic aspects of known allergic processes.

THE HOST

As with many diseases which attack with some degree of discrimination rather than haphazardly as does a wild contagion, rheumatic fever appears to occur in individuals predisposed by some feature of their constitution. The incidence of multiple cases in a family is sufficiently common to suggest that this feature is probably hereditary.^{62,199,212,280} Wilson and her co-workers have applied classical techniques of genetic analysis to this problem. They calculate that the predisposition to rheumatic fever occurs in 5 per cent of the population and that it is inherited through a single autosomal gene, as a Mendelian

recessive characteristic. However, the possibility that similar environmental factors may be exerted, even through a number of generations, has not been excluded and, indeed, has been suggested by many studies.^{180,199,212} Wilson²⁸⁰ states "Final conclusions on the role of environment do not appear possible until data are available on the familial incidence of rheumatic fever among the well-to-do."

The characterization of a predisposed constitution does not exclude the possibility that individuals ordinarily not predisposed and with no family stigmata may nevertheless exhibit the same pathologic reaction under unusual circumstances. Epidemics of rheumatic fever have been described in which from 10 to 30 per cent of individuals with an acute tonsillitis developed acute rheumatic fever.^{18,59,93,288} Such epidemics were particularly well documented at training camps during the recent war, and are of special interest because many of the known rheumatics had been disqualified from service.^{211,259,271} Holbrook¹¹⁸ reported that the incidence rates for the year 1943 were in excess of 25 per thousand troops at some air bases. During the peak of the rheumatic fever season one large post in Colorado experienced a rate of rheumatic fever in excess of 100 per 1,000 men annually. If the subclinical attacks of rheumatic fever, as evidenced by changes in sedimentation rate or electrocardiograms, are included, the rates may be still higher.^{209,271}

* From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital, New York, N. Y. This work was done during the tenure of a Life Insurance Medical Research Fellowship, and was aided in part by the Masonic Foundation for Medical Research and Human Welfare.

How the constitutional predisposition noted in usual civilian practice is effected is not known. Several possibilities exist which have their analogies in studies on experimental animals and on humans. These include the inheritance of some qualitative or quantitative alteration in the host's ability to cope with infection, a predisposition to allergy and an alteration in the end organ affected, in this instance the host's connective tissue system. Inherited strain differences in degree of resistance to infection have been well studied in guinea pigs¹⁶⁰ as have variations in ability to produce antibodies,^{152,264} to become passively sensitized;²⁸⁵ and to become actively allergic.²⁸ Rheumatics have generally failed to give a personal or family history of increased incidence of allergies such as hayfever or eczema. A greater frequency of reactions to sulfanilamide^{174,251} and to non-specific skin tests²²⁷ has been reported but was not noted in another series⁹¹ and has not been recognized with the use of the newer antibiotic agents (personal observations).

In addition, the host's contribution to the illness has been suggested by various studies on dietary deficiencies, particularly in relation to vitamins A and C and proteins.^{43,218} These have not been confirmed, however, and the deficiencies have not been shown to differ from alterations occurring in many acute and chronic febrile illnesses. The disease is extremely variable from case to case, and from time to time in the same case. It is, moreover, difficult to make a quantitative appreciation of dietary habits. Therefore, studies on both these variables, the disease and the diet, are difficult to control and evaluate.

Before leaving the consideration of host factors, it should be noted that clinical rheumatic fever may, in a sense, be a magnification of processes that occur to a lesser degree in many individuals recovering from a streptococcal sore throat. It is difficult to draw the line between clinical rheumatic fever and the cases of pharyngitis which continue to have a low fever, a few transient electrocardiographic changes or a mildly

elevated sedimentation rate for longer than the usual period of time. The existence of 28 to 50 per cent of 2,500 cases of rheumatic valvular disease without a history of previous recognized rheumatic fever,¹⁵¹ emphasizes the inadequacy of any attempted differentiation between the apparently minor changes and the full blown rheumatic syndrome. No adequate history of acute rheumatic fever was found among a similar percentage of women with organic valvular disease at the Boston Lying-In Hospital.¹⁰³ Rantz, et al.²⁰⁹ found that about one-third of 185 men with streptococcal sore throat had electrocardiographic changes, elevated sedimentation rate or some manifestation of "continuing disease." Twenty-one of the 185 had electrocardiographic changes similar to those of acute rheumatic fever but only nine had arthritis and were clearly diagnosed as acute rheumatic fever. Watson, Rothbard and Swift²⁷¹ found that of 110 cases of scarlet fever eight developed frank rheumatic fever, but eleven others had changes which they considered qualitatively, although not quantitatively, to be those of rheumatic fever. With reference to the occurrence of subclinical pathologic phenomena following streptococcal infections, it is of interest to recall Lyttle's studies in fourteen cases of scarlet fever.¹⁶² He found that all the patients developed a sudden explosive increase in urinary red cells, white cells and casts, by Addis count, about two weeks after the onset of scarlet fever although none developed clinical acute nephritis.

THE AGENT

Many features of acute rheumatic fever resemble aspects of infectious disease. Investigators have naturally sought for an infectious agent as the cause of the rheumatic state. Various organisms have been suggested, including viruses, a virus-streptococcus combination, the tubercle bacillus and various kinds of streptococci.

A virus as the etiologic agent was proposed by Aschoff because the typical myo-

cardial lesions suggested to him the reactions to viruses at other sites in the body. However, the early lesions in rheumatic fever involve the extracellular connective tissue and the later infiltration appears to be a secondary phenomenon. In this selectivity for connective tissue and in its intercellular localization, the pathology of rheumatic fever is unlike that of known virus infections.²⁵⁰ The virus hypothesis gained in popularity for a time when Schlesinger et al.²²⁵ found particles resembling elementary bodies in pericardial fluid. Although these particles were agglutinated by sera from rheumatic patients, subsequent work by Eagles and Bradley⁶³ showed that such particles were non-specifically agglutinated by sera from various types of arthritis, including gonococcal. Attempts to transmit the "virus-like bodies" to monkeys were unsuccessful.⁶⁴ In 1945 MacNeal et al. claimed to have transmitted a virus from the blood and pericardial fluid of rheumatics to animals and chick embryos.¹⁶⁸

In animals, various viruses, pleuropneumonia-like organisms and other agents have been found to cause myocarditis but no association with clinical rheumatic fever could be established.^{153,200,222,246}

The demonstration that a streptococcus could not effectively establish itself when instilled onto the nasal mucosa of ferrets unless an influenza virus infection was present⁵ is of interest in view of the suggested symbiotic virus-streptococcus relationship in rheumatic fever. However, attacks of influenza and common cold unaccompanied by streptococcal infection have not given rise to rheumatic fever while epidemics of streptococcal tonsillitis, apparently unassociated with virus infection, have resulted in appreciable attacks of rheumatic fever.^{36,51,93,213}

It has been stated that the tubercle bacillus is the causative agent of rheumatic fever, particularly in the European literature.¹⁵⁴ While the work on which this hypothesis is based has not been reproducible, it is nevertheless of interest in this discussion

because tuberculosis and allergy to the tubercle bacillus have frequently been used as patterns for hypothesis and investigation of the role of the streptococcus or other agents in rheumatic fever. Tuberculin reactions can be produced in various visceral sites in tuberculous animals. The resulting lesions are similar to the non-specific cellular infiltration that occurs in the various attempts at the experimental production of rheumatic fever. The occurrence of Aschoff-like bodies in tuberculous hearts has been reported.^{110,178}

There is now overwhelming evidence that most cases of rheumatic fever can be related to a preceding infection with a hemolytic streptococcus. Acceptance of this relationship has been slow but it is now widespread.

In 1880 Heberden described rheumatic fever and noted that it usually followed acute tonsillitis. In the same year Fowler reported twenty cases of acute rheumatism preceded by tonsillitis. Five years later Mantle reemphasized this relationship and spoke of rheumatic fever as a common complication of infectious sore throat.⁹³ It remained for Chacdle to present in 1889 the vagaries of clinical rheumatic fever in his classic monograph.²⁷

With the application of bacteriologic techniques the streptococcus was found to be the most prominent organism in the pharyngeal flora preceding the rheumatic attack. Investigators were first interested chiefly in the *Streptococcus viridans* and a non-hemolytic streptococcus.^{11,205,241,247,276} After attention had been focused on the *Streptococcus hemolyticus* in scarlet fever,⁶⁰ and an antigenic classification of the streptococcus became possible,¹⁴⁷ three reports appeared in England and in the United States which incriminated the hemolytic streptococcus, particularly of Lancefield's group A.^{36,51,221} Coburn presented impressive epidemiologic, bacteriologic and immunologic evidence relating the *Str. hemolyticus* to the infectious process which precedes the development of most of the cases of rheumatic fever.^{36,44,45} Since that

time a voluminous literature of confirmatory reports has accumulated.

Bacteriologic and epidemiologic studies have been made of numerous epidemics of sore throat followed by an appreciable incidence of rheumatic fever.^{18,44,59,93,207,259,271} The seasonal incidence of hemolytic streptococcus infection has been found to parallel the incidence of rheumatic fever. Coburn³⁶ cites many references to show the geographic coincidence of the two diseases but this relationship is not as constant as the seasonal incidence. In 1935 Seegal, Seegal and Jost reported that the incidence of acute glomerulonephritis was similar in northern and southern latitudes but that the incidence of hospital admissions for rheumatic fever and scarlet fever was lower in the South.²³⁶ These discrepancies have been resolved somewhat by recent evidence that rheumatic stigmata are rather commonly found at autopsy in tropical countries, and that clinically the disease appears to be much less dramatic in its symptomatology. In addition there is a reported increase in the incidence of rheumatic fever at autopsy in certain tropical countries.^{80,105,109,203,277} Rheumatic fever seems to be appreciably frequent in North Africa.¹³

Many cases of rheumatic fever (about 70 per cent in the early studies of Poynton) present themselves with no history of a preceding sore throat. The existence of a subclinical streptococcal infection can frequently be detected by the demonstration of antibodies to many of the antigens of the streptococcus. One of the most widely employed of these is the antibody to the streptococcus hemolysin "O," defined as a serologically distinct entity by Todd.²⁶¹ About 80 to 90 per cent of rheumatics studied in many different countries show a rise in the antistreptolysin (ASL) titer.^{44,45,94,133,191,207,256,263,282} At first a pathognomonic type of curve with a delayed rise was thought to occur in rheumatic subjects but more recent studies have shown no consistent type of curve. Moreover, a slowly rising curve was found to occur in many other streptococcal infections in which the

antigen is found to persist, as in otitis media and other subacute and persistent infections.^{96,146,191,256,282}

Antibodies to other antigens derived from the Str. hemolyticus have also been found in acute rheumatic fever. The antifibrinolytin, or antistreptokinase of Christensen and MacLeod,³¹ has been studied extensively as evidence of previous infection with hemolytic streptococci in rheumatic individuals.^{4,16,100,192,260,282} In addition, skin sensitivity, precipitins and complement-fixing antibodies have been found to "nucleoprotein" fractions of the streptococcus, although with increasing age a fair percentage of normal individuals also show skin sensitivity to these fractions.^{11,36,91,106,134,169,232,253} Skin sensitivity and precipitins to the type specific "M" substance have also been described.^{48,248,255} None of these antibody responses appears to differentiate the rheumatic from other individuals with infections due to the Str. hemolyticus. It has been reported that the antibody response to the "S" hemolysin is less marked in rheumatics²⁶³ although the differences were not striking. The extreme lability of the substances involved in this reaction makes extensive study difficult. Rantz and Randall²⁰⁸ reported the increased frequency of an "anti-x" antibody in post-streptococcal arthritis as compared with other post-streptococcal conditions. As yet there has been no adequate definition of the nature of the reported antigen to permit critical comment.

Finally, evidence relating the Str. hemolyticus to the development of rheumatic fever is obtained from the prophylactic use of antibiotics such as the sulfa drugs^{41,145,257} and penicillin.¹⁷² The administration of sulfadiazine to naval trainees was accompanied by a diminution of 85 per cent in the incidence of acute tonsillitis and of rheumatic fever when compared to the incidence in control groups.³⁸ With the appearance of sulfa-resistant strains in some localities tonsillitis and rheumatic fever recurred, exhibiting their usual relationship to each other.

No particular strain or type of group A streptococcus has been shown to have the exclusive property of initiating a rheumatic attack.²²⁰ The admirable epidemiologic studies of the Army Air Forces Rheumatic Fever Control Program revealed that infection with various types was associated with the subsequent development of rheumatic fever.¹²⁵ Indeed it has been suggested that rheumatic fever may be caused by infection with one type, followed by a subsequent infection with another type of hemolytic streptococcus.^{125,207} In several epidemics of streptococcus sore throat it was found that the incidence of rheumatic recrudescences was 40 to 60 per cent with all types encountered except Type 4. Infection with the Type 4 streptococcus was followed by no attacks of rheumatic activity in these epidemics.¹⁴⁶ Organisms of this type were found to lack capsular material. One substance known to be present in the capsule is the mucopolysaccharide, hyaluronic acid.¹⁸³ It is peculiar that this substance, although widely distributed in the connective tissue and related mesenchymal structures of animals, is present in only one bacterium, the mucoid phase of the *Str. hemolyticus* of all types except 4 and 22. As yet, many attempts to detect antigenicity in hyaluronic acid have been futile.^{52,71,122,137,229}

Despite the mass of evidence linking the hemolytic streptococcus to the rheumatic process, the latter cannot be visualized merely as a kind of infection with the streptococcus but appears to involve other determining mechanisms. That the streptococcal infection *per se* does not constitute the rheumatic process is apparent from the following observations: (1) In rheumatic conditions the joint fluids and blood stream are usually sterile.²⁸⁶ (2) The frequency of infection with *Str. hemolyticus* is not paralleled by a similar frequency of rheumatic fever. (3) The severity of the streptococcal infection bears no relation to the severity of the subsequent attack of rheumatic fever. Treatment of the streptococcal infection once it is established has little apparent effect on the development of the subsequent

rheumatic attack. (4) In almost all series of rheumatic fever cases there is a small percentage with no history or laboratory evidence of a preceding streptococcal infection. In addition, recrudescences have been observed following various types of trauma,¹²⁶ splenectomy^{16,132} and typhoid inoculations.¹⁴ Suggestive lesions occur in humans with other infections.^{110,178} (5) Streptococcal infection alone cannot constitute the rheumatic process because such infection occurring in known rheumatic subjects is *not* followed by a recrudescence of activity in as many as 50 to 60 per cent of the cases.^{42,146} (6) Finally, the lack of chronologic coincidence of the two processes speaks against the identity of rheumatic fever and the infectious process. The latent period between the occurrence of acute tonsillitis and the onset of rheumatic fever was first noted by Haig-Brown in 1899.⁵¹ "An attack of acute rheumatism is very frequently preceded by one of acute tonsillitis; it may be as long a time as five or six weeks but more usually ten days to a fortnight, while as has been already stated, the two may be coincident in time. In fact, it is rare to meet a case of rheumatic fever which has not been recently preceded by a sore throat." It is for these reasons among others that attention was directed away from the infectious process alone and toward the allergic process resulting from it, as the possible cause of rheumatic fever.

THE REACTION

Many observers have suggested that rheumatic fever may be the result of an allergic mechanism. Menzer in 1902 suggested that rheumatic fever displayed certain unusual manifestations which could not be ascribed simply to an infectious process. He is credited with being the first to advance the theory of an allergic type of mechanism at a time when allergy was scarcely defined. Because rheumatic fever resembles the clinical picture of serum sickness, a disease which was the subject of a classic monograph by von Pirquet and Schiek,²⁰¹ Weintraud²⁷⁵ believed that an allergic process

was common to both diseases. In the same year (1912) Escherich and Schick suggested an allergic mechanism after observing that the latent period for the development of rheumatic fever following scarlet fever was similar to that period necessary for the production of active sensitization or immunization.⁶⁹ In 1914 Herry produced lesions similar to Aschoff nodules by repeated local and intravenous injections into rabbits with an "endotoxin of diplococci" obtained from cases of rheumatic fever. On this basis he subscribed to the allergic hypothesis. His illustrations are rather impressive.¹¹⁶ He states that his experiments "me paraissent éclairer singulièrement la pathogenie de l'arthrite rhumatismale; elles permettent de l'envisager d'une façon toute nouvelle, grâce à la théorie de l'anaphylaxie. Pour moi, l'arthrite rhumatismale serait un phénomène d'anaphylaxie locale."

The experimental study of certain allergic reactions has led many investigators to conclude that an analogous process may result in the tissue damage which is clinically manifested as the rheumatic state. These investigators include Zinsser,²⁸⁶ Swift,^{244, 245} Klinge¹⁴¹ and more recently Brun,²¹ Rich²¹⁴ and others.

Too often the term "allergy" brings to mind clinical diseases such as hayfever and urticaria. These transient manifestations of the union of certain antigens with their antibodies should be distinguished from the necrotizing types of allergic reactions of which the chief prototypes are the Arthus reaction and the tuberculin reaction.^{88, 286} Because these reactions cause tissue damage and subsequent cellular infiltration not unlike that which occurs in some rheumatic lesions, it was believed of particular interest that the mechanisms of these be elucidated. In the absence of a method for experimentally inducing rheumatic fever, these reactions provide an hypothetical analog of the rheumatic state. It would be of interest to consider in detail the Arthus reaction, bacterial allergy and a third type of reaction, isosensitization.

The Arthus Reaction and Serum Sickness.

The Arthus reaction is a localized necrotic inflammatory response to the union of certain antigens with antibody. It is similar in many respects to anaphylaxis and has unfortunately been called local anaphylaxis with no little confusion of terminology. In each reaction circulating antibody is demonstrable and bears a distinct relationship to the production of the particular lesions. The quantitative relationships of the two reactions have been reviewed by Kabat.¹²⁹ Anaphylaxis is in part mediated by histamine or some similar substance, presumably released from cells in the presence of the antigen-antibody complex.²⁶⁴ The end organ in anaphylaxis is smooth muscle, particularly in one or another locale according to the species of animal studied.²³⁰ In the rabbit the Arthus reaction appears to affect the smooth muscle of the blood vessels.¹ The Arthus reaction, originally produced in the skin, is a more intense and persistent process of an inflammatory nature. By the use of a single protein antigen and known amounts of the homologous antibody, as determined by the quantitative precipitin technic of Heidelberger and Kendall, it has been demonstrated that the severity of the Arthus lesion appears to be directly related to the amount of antibody available to the site of injected antigen.⁷⁵ The Arthus reaction has been most widely studied in the skin but it reflects the union of antigen with antibody at any site in the body. Friedberger⁸³ was the first to produce an aseptic arthritis by the intra-articular injection of a foreign protein, horse serum, into sensitized rabbits. Since then the Arthus type of reaction has been produced experimentally in many sites, including heart and pericardial sac,^{9, 156, 235} joints,^{21, 140} brain,⁵³ kidney,¹⁵⁵ eye,²³⁴ lungs,^{24, 82, 97} liver,^{108, 155} isolated blood vessels¹⁸⁴ and even the vermiform appendix.⁷⁸ Other studies of local hypersensitivity in different sites have been reviewed by Seegal, Seegal and Jost.²³⁵

Clinically the Arthus reaction has its parallel in serum sickness in which residual antigen is known to unite with antibody throughout the body.^{127, 157, 158, 170, 204} Clark

and Kaplan demonstrated mesenchymal alterations occurring in serum disease in man.³² Generally the lesions were not as dramatic as those found in experimental work. Besides the local Arthus reactions mentioned above, numerous studies have been made of the systemic or serum sickness type of reaction after injections of foreign proteins into animals. In 1917 Boughton injected guinea pigs with egg white or beef serum repeatedly and found degenerative lesions in all of the livers and spleens and in two-thirds of the kidneys and hearts.¹⁷ Klinge and his school have published extensively on this type of experimental procedure, particularly in Virchow's Archiv 1929-1939. The "hyperergic reaction" is a supposed "morphological equivalent" of rheumatic lesions.²²⁰ The list of other workers who have employed the serum sickness type of technic locally and systemically includes Vaubel,²⁶⁷ Roessle,²²⁰ Brun²¹ and Rich.²¹⁴ Of particular interest is the work of Hawn and Janeway.¹¹¹ These investigators injected different fractions of plasma proteins—crystalline bovine albumin and highly purified gamma globulin—into rabbits. The former substance resulted in periarteritis-like lesions while the globulin gave predominantly renal lesions. The temporal relationships also differed in the development of these lesions, much as they did in the work of Doerr and Berger.²³⁰ Serologic reactions appear to have a specificity not only *in vitro*¹⁴⁸ but, to a certain degree, *in vivo*.

Bacterial Allergy and Tissue-fixed Antibodies. The tuberculin reaction is the prototype for the bacterial allergic reaction.^{88, 284, 286} It is not transferable with serum of the sensitized animal nor can precipitins be demonstrated in the serum. Rather, it appears that the sensitizing agent, an antibody in the true sense of the word, is fixed to cells of the host. Washed cells from a peritoneal exudate can transfer the sensitivity²³ and in this respect it is similar to the allergy to simple chemical compounds.¹¹³⁻²²⁸ Sensitive white cells are lysed by exposure to the antigen⁷¹ and the growth of connective tissue or bone marrow

cell cultures can be inhibited by exposure to the specific antigen.^{6, 217} Cell cultures from an animal sensitive to horse serum and tuberculin were affected only by the latter.⁶ The specificity of the reaction has been corroborated.¹⁸⁸ Similarly the cells of animals sensitive to a "nucleoprotein" extract of streptococci were found to be inhibited by exposure to this antigen.¹⁸⁷ Lurie's work¹⁶¹ in this connection is particularly pertinent. Mononuclear cells from rabbits immunized to tuberculous infection preserved their power to inhibit the growth of tubercle bacilli when transplanted to the anterior chambers of normal rabbit eyes. Similar cells from normal rabbits did not possess or acquire this property, even when placed in the anterior chamber of the eye of an "immunized" animal or suspended in the serum of such an animal.

The lesions produced in the Arthus and tuberculin reactions are the subject of some discussion. Opie described multiple small thromboses as the basic lesion in the Arthus reaction which then cause cell death secondarily and subsequent polymorphonuclear leukocytic infiltration.¹⁹⁶ This is in accord with Gerlach's observation that the Arthus reaction is not dependent on the leukocytic infiltration but can occur in agranulocytosis.⁹⁰ The tuberculin reaction has been described by Dienes and Mallory as chiefly mononuclear in character, even early in the development of the lesion.³⁷ This was confirmed by Lurie¹⁶¹ and by Feldman and Fitch,⁷² but Rich and Folli²¹⁵ found that polymorphonuclear cells predominated. Sabin²²³ has shown very impressively that different cellular infiltrations result when various fractions of the tubercle bacillus are injected into sensitized animals. It would appear that the reaction depends on the chemical constitution and toxicity of the antigens employed, the amount of antigen and antibody uniting, the speed of the reaction and the site at which it occurs. These observations again emphasize an aspect of the specificity of immunologic reactions *in vivo*.

Not only can the antibody of the tuber-

culin reaction be demonstrated on the cells of the host but the cells of the inflammatory reaction appear to be responsible in great part for the production of this particular type of allergic reaction. Antigens which ordinarily produce circulating antibody and an edematous wheal and erythema type of response are said to have elicited a tuberculin type of response.^{58,104} If egg albumin is injected into a tuberculous focus, the subsequent injection of egg albumin does not elicit the same type of reaction as is induced in animals sensitized to egg albumin according to the usual technique. Rather a delayed reaction results, similar to the tuberculin or severe Arthus reactions. The production of an increased amount of antibody to egg albumin injected into a tuberculous site may account, in part, for the stronger reaction.^{75,81} The route of sensitization is known to affect the type of allergic response, the potency of the antigenic stimulus and the type of antibody produced. Thus the intravenous administration of antigens was found to result in an immune type of skin reaction to the antigen, while subcutaneous administration resulted in an allergic inflammatory skin test.¹⁵ The C substance of the streptococcus is an effective antigen when introduced intravenously but not subcutaneously.²³³ Using rabbit globulin, Treffers, Heidelberg and Freund²³ showed that intravenous administration in the horse resulted in a characteristic precipitable antibody. The subcutaneous administration of the same antigen gave rise to low grade "univalent" antibody which did not precipitate with the soluble antigen.

These studies are in accord with the view that antibodies are not produced by any single cell type but may be elaborated by almost any cell exposed to the proper stimulus. Local tissue immunity has been the subject of many investigations.⁸⁷ Many cells, including the highly specialized cells of the central nervous system^{120,130,190} the skin epithelium⁷⁶ and mucous membranes²⁶⁹ have been thought to retain certain basic mechanisms such as sensitization to previ-

ously encountered noxious stimuli. Antibody has been clearly demonstrated in corneal tissues sensitized locally when no circulating antibody was demonstrable.²⁵⁸ It should be emphasized that all these cells need not contribute to the circulating antibody. The latter may well originate from certain cell types,²³ particularly the cells of the reticulo-endothelial system^{88,89} plasma cells,¹² and perhaps other cells in the lymph nodes.^{61,66,167} Such cells appear to have potentialities to become various cell types of mesodermal origin. The inflammatory cells of the classical rheumatic lesion, the Aschoff nodule, may belong to this cytologic family.^{33,98,165,166}

The tuberculin reaction has served as a pattern for attempts at the experimental production of rheumatic fever. When living organisms are injected, it is not unlikely that the resulting disturbance may in part be due to an allergic reaction; however, the damage done by the living organism and its toxins frequently confuses the picture. It is therefore easier to evaluate lesions in which only the sterile products of organisms or killed organisms are employed. Magrassi¹⁷¹ reported that the repeated injection of dead streptococci gave lesions highly suggestive of rheumatic fever. Subsequently, it is stated that some of his lesions may have been due to septicemia.²¹⁰ Faber⁷⁰ in 1915 and later Hitchcock, Camero and Swift¹¹⁷ used repeated injections of living and dead streptococci, as did Clawson,³ and obtained some perivascular and granulomatous lesions. Recently Swift^{245a} showed that repeated intradermal infections of rabbits with hemolytic streptococci occasionally resulted in striking cardiac lesions. A pathway for the experimental production of rheumatic fever is indicated by this type of study if it were demonstrated that non-viable fractions of the streptococcus could produce such lesions, and that infections with other organisms did not result in this type of reaction. When tubercle bacilli were injected into the peritonsillar region of rabbits and the animals subsequently injected intravenously with the organisms, lesions of a rheumatic nature were also reported.³ Products of the strepto-

coccus and other organisms have been used for the production of visceral and vascular lesions of allergy.^{116,257} After an extensive review and original work, Gross, Locwe and Eliasoph concluded that lesions produced by this type of technic are not characteristic rheumatic lesions.⁹⁹

Both the Arthus and tuberculin types of reaction have been employed as basic patterns for attempts at the experimental production of rheumatic fever. While these studies are not conclusive and have been challenged,⁷ they are highly suggestive. They demonstrate that allergic reactions of the necrotizing variety can be produced in this way and that in certain instances and certain sites particular cells may be intimately sensitized without evidence of such sensitivity in the serum, as in the tuberculin reaction. The pattern for the suggested pathogenesis of rheumatic fever thus has a foundation in the basic mechanisms of these allergic reactions.

Isosensitization and Autosensitization. Other techniques have been employed in the study of the pathogenesis of rheumatic fever. The Arthus technic classically employs a foreign antigen and the host's antibody, and the reaction may occur on any tissue surface, with damage to the cells of that vicinity. When the surface itself is made the antigen, a more selective lesion may obtain. The studies of Masugi,¹⁷⁷ Smadel and Farr²⁴⁰ and Seegal and Loeb²³¹ on nephrotoxic nephritis basically employ the host's tissue (kidney or placenta) as antigen and use a heterologous antibody. Attempts to do the same, using heart or connective tissue as antigen, have proved less fruitful.^{10,52,73} One of the constituents of connective tissue is the mucopolysaccharide hyaluronic acid.¹⁴³ Unsuccessful attempts have been made to detect antibodies to this substance. It has been suggested that the failure of hyaluronic acid to function as an antigen or hapten might be accounted for by the fact that the substance occurs normally throughout the mammalian organism.^{12,74,122,127,227}

Finally, attempts have been made to employ antigen and antibody derived from the

same species—the autoantibody system. In 1933 Burky found that rabbits sensitized to staphylococci also developed sensitivity to the muscle tissue of the broth in which the staphylococci were grown.²² The observation was extended and it was found that staphylococcal toxin exerted a type of adjuvant, or synergistic effect, which conferred a greater power of antigenicity to rabbit muscle, lens and uveal tissue in rabbits.¹⁵⁹ The observation that rabbits do have a circulating autoantibody¹³⁸ has been attributed to the fact that only the older rabbits displayed these antibodies, and they presumably had had infections which may have produced the phenomenon naturally.¹²⁸ Generally the streptococcus has not been as potent an adjuvant as the staphylococcus.^{228,252} However, Cavelti reported that dead streptococci mixed with rat kidney produced autoantibodies and renal lesions similar to glomerulonephritis in rats. His report on the parallel technic for the production of autoantibodies to rat heart²⁶ does not have as dramatic illustrations as those of renal lesions. In our experience the results of this type of experiment are inconsistent. The most frequent lesions encountered were granulomas of the lung.⁷¹ These and other abnormalities occurred with Freund's emulsion and tubercle bacilli alone. Recently, Peek and Thomas reported the failure to produce rheumatic-like lesions using tissue extracts, streptococci and adjuvants.²⁰¹ The analogous experiment with homologous brain tissue and the adjuvants of Freund and McDermott⁸¹ produces striking lesions in the central nervous system of monkeys.^{131,189}

Clinically, isoantibodies do frequently cause damage to humans in such situations as erythroblastosis fetalis, the Donath-Landsteiner phenomenon, acquired hemolytic icterus and occasionally cold agglutination. However, the commonly observed Wassermann antibody in syphilis is an antibody to a constituent of normal tissues^{34,45,271} and does not appear to produce widespread tissue damage, nor does the naturally occurring antibody to rabbit tis-

sues appear to be a detrimental influence to the rabbit.¹³⁸

Lack of Specificity of the Pathology of Necrotizing Allergies. The criteria for the establishment of the relationship of allergy to certain infectious diseases have been discussed by Opie.¹⁹⁷ Substantial difficulties are present in any attempt to ascribe an allergic basis for the manifestations of readily diagnosable infectious diseases. In the consideration of rheumatic fever these difficulties are increased by the additional uncertainty attendant upon the clinical definition of the rheumatic state. Reports of the experimental production of rheumatic fever have met with several cogent criticisms. Unfortunately, the diagnosis of rheumatic fever clinically does not involve any single pathognomonic finding. In animals the criteria for the production of the rheumatic state are even more confusing and usually rest on the lesions produced. Again and again it becomes necessary to recall the axiom that the body can react in but a limited number of ways to numerous and varied stimuli. Viruses may cause cell proliferation or cell death, with attendant secondary effects on blood supply and cellular infiltration. Various other infectious agents, neoplasms and physical stimuli can cause similar pictures. Many chronic infections and some acute ones present the well known perivascular accumulation of lymphocytes and mononuclear cells. Experimentally and clinically, this has been seen with all types of pyogenic bacteria, acid-fast bacilli, viruses, etc.^{2, 19, 79, 144, 173, 194, 239, 266} Oeller¹⁹⁵ showed that perivascular accumulation of mononuclear cells occurred within an hour after injection of avian erythrocytes into guinea pigs. In acute reactions the perivascular and intravascular lesions resemble those of periarteritis nodosa.^{143, 182, 216} Such lesions have been found in a variety of conditions such as asthma,²⁷⁹ gonococcal septicemia¹¹⁴ and sulfa sensitivity.²¹⁴

This lack of versatility on the part of the body in reacting to many injuries is emphasized by students of Klinge and more

recently by Klemperer¹³⁹ and Selye.²³⁷ The criteria for the establishment of an allergic process as the cause of a disease cannot, therefore, be as specific as the criteria postulated by Koeh for the determination of the etiologic agent in infectious disease.¹⁹⁷ However, within limits, there does appear to be a certain specificity of immunologic reactions *in vivo*, as was noted previously.

Rheumatic fever has been diagnosed by a number of morphologic changes:^{92, 164} (1) There is, at first, swelling and "fibrinoid" degeneration in the ground substance surrounding the connective tissue fibrils.^{140, 141, 254} (2) The site of the reaction is chiefly in the connective tissue, usually in the septa of the heart and around blood vessels although there is adequate clinical and pathologic evidence that the disease is widespread throughout the body.^{142, 164, 198} (3) Round cell infiltration of a non-specific nature occurs, as discussed above, along with proliferation and hyperplasia of the connective tissue cells and the appearance of "specific" Aschoff cells. These latter cells may be a type of plasma cell or a derivative of the cardiac connective tissue cell.^{7, 8, 67, 98, 163, 243} The specificity of these cells, so strongly maintained by Aschoff,⁷ is open to question. (4) Finally, hyalinization and scar formation occurs in the collagenous septa or in the connective tissue of the cardiac valves.

The sequence of these lesions has been debated⁵⁰ but each or all of them are used by experimental workers as criteria for "rheumatic" activity. However, these lesions can be produced singly or in combination by various stimuli: physical (pinching the skin²⁸³), chemical (allyl amine,⁶⁸ benzpyrene,¹⁵⁰ nitrites¹²¹), hormonal (adrenal hormones,^{202, 237} thyroxine,¹⁸¹ pitressin,¹⁹³), and other stimuli.¹³⁹ Various infections, as previously stated, and in addition "malignant" hypertension,^{30, 237} scurvy^{163, 219, 226} and other severe systemic illnesses give rise to some of these lesions. Indeed, these stigmata may be quite common, for Hall and Anderson report that rheumatic stigmata were found in about 90 per cent of 112 hearts

studied minutely although none showed evidence clinically or grossly of rheumatic fever.¹⁰² "Spontaneous" cardiovascular lesions occur frequently in rabbits and rats^{153, 278} and are probably the result of naturally occurring infections. Chronic valvular disease, similar to that produced clinically by rheumatic fever, has not been produced by the experimental procedures discussed above. This lesion has been obtained only after the use of living organisms, which presumably cause an acute septic endocarditis and then a healed or chronically infected scarred valvulitis.³⁵

Subcutaneous nodules and erythema nodosum are other lesions which have been studied in an attempt to elucidate the mechanism of production of the rheumatic state. Here again there is a lack of specific histologic character and a variety of clinical and experimental conditions associated with the appearance of these lesions.¹³³ These preclude a definitive statement concerning the specific role of the experimental procedures said to induce the lesions. Trauma and the subcutaneous injection of the patient's own blood have been employed to induce the formation of subcutaneous nodules¹⁷² but another investigator failed to repeat this observation.¹⁰⁷ Injections of a proteolytic enzyme have also been reported to stimulate the formation of subcutaneous nodules.¹⁸⁶ Subsiding erythema nodosum was reactivated in tuberculous patients by the injection of old tuberculin.¹⁰ A similar phenomenon has been observed in rheumatic subjects injected with streptococcal nucleoprotein.⁴⁰

CLINICAL STUDIES CONCERNING THE ALLERGIC MECHANISM IN RHEUMATIC FEVER

The evidence that an allergic type of mechanism may produce the rheumatic process is strongly suggestive but, as yet, only suggestive. It is based chiefly on the clinical aspects suggesting allergy (latent period, etc.) previously cited and the morphologic analogy between rheumatic lesions and those produced by necrotizing allergic reactions in experimental animals.

Clinical studies of rheumatic patients have usually served to substantiate the occurrence of a preceding streptococcal infection by documenting the appearance of circulating antibodies or skin sensitivity in rheumatic patients. However, these responses do not appear to differ qualitatively or quantitatively from those of normal individuals with streptococcal infections, particularly if the infection is persistent. To determine the antigens or antibodies involved in the presumed allergic reaction would serve to establish a pathognomonic basis for the allergic hypothesis. There are relatively few reports on work of this type. These are chiefly concerned with attempts to demonstrate antibodies in rheumatic patients not found in other individuals recovering from streptococcal infections.

The Phase Reaction. In 1939 Coburn and Pauli reported that following a sore throat in a rheumatic subject a substance called a "precipitinogen" appears in the serum and precipitates with a component of the serum taken during the subsequent rheumatic attack.⁴⁹ Because the reaction appeared to occur when serum taken during phases I and II (the sore throat and the latent periods) was mixed with serum from phase III (the period of rheumatic activity), it has been called the "phase reaction." Wedum and Wedum confirmed some of these observations but found a greater degree of non-specificity for the reaction and a different time relationship for the appearance of the presumed antigen and antibody.²⁷³ This phenomenon was further studied with various control tests⁷⁷ and was found to be non-specific and irregularly reproducible. Further, it appears that when precipitation does occur it does not present the characteristics of the usual precipitin test nor lend itself to passive transfer, dilution or complement fixation tests. It cannot, therefore, be considered an antigen-antibody reaction.

Autoantibodies in Rheumatic Fever. Other clinical findings suggesting an allergic mechanism in rheumatic fever have been reported. The concept of an autoantibody in rheumatic fever was suggested by Brok-

man, Brill and Freundzel.²⁰ These investigators found that sera from rheumatic patients fixed complement when mixed with an extract of liver obtained at the autopsy of a rheumatic individual. Sera from other diseases did not fix complement with this "antigen." Unfortunately, anti-complementary controls were not reported. It is well known that tissue extracts are frequently anticomplementary, as are, occasionally, rheumatic and other sera in certain concentrations. Complement fixation is reported to occur with liver tissue and the sera from some normal individuals as well as those with a variety of illnesses.⁶⁵ In our experience⁷⁷ no evidence of complement fixation was found in dilutions of rheumatic serum and of tissue extracts that were not anticomplementary alone. If complement fixation occurred, it would be difficult to distinguish the reaction from a non-specific false positive Wassermann type of reaction. The same criticism applies to many attempts to demonstrate autoantibody reactions with tissue extracts. Cavelti²⁵ employed the collodion particle technic to detect agglutination of antigen by antibody. One of four normal (i.e., non-rheumatic) hearts used as antigen reacted strongly with sera from twenty-seven of thirty-six rheumatic patients studied. Subsequently Cavelti could not reproduce the phenomenon with other heart preparations (personal communication).

Using the technic of Cavelti it has been observed that collodion particles coated with various tissue extracts, particularly from lung, kidney and tonsil, were agglutinated by a few rheumatic sera but more regularly by syphilitic sera.⁷⁷ Therefore, the possibility continues that the reaction noted is similar to a biologically false positive flocculation test for syphilis. It is of interest that the Wassermann antigen is a constituent of normal tissue.^{54,274} The occurrence of biologically false positive Wassermann reactions in many diseases has been reviewed by Davis.⁵⁴ Another possible explanation of the positive reactions is that bacterial contamination of the tissues used may serve as

antigens for antibodies in the sera. Thus, collodion particles mixed with an extract of tonsillar tissue were regularly agglutinated by some sera as might be anticipated since the tonsils had been infected with hemolytic streptococci.⁷⁷

Serum Complement in Rheumatic Fever. The fixation of complement by many antigen-antibody aggregates in the test tube (phenomenon of Bordet and Gengou⁸⁸) suggested a third experimental approach to the documentation of an allergic process in rheumatic fever. Serum complement, normally maintained with little variation, has been observed to fall in anaphylactic shock⁸⁴ when sheep cells and amboceptor are injected into guinea pigs¹²³ and in serum sickness.²²¹

In the study of rheumatic fever there has been disagreement and confusion as to the activity of serum complement. Veil and Buccholtz,²⁶⁸ Coburn,³⁷ Rachmilewitz and Silberstein²⁰⁶ and others have reported a low complement content of the serum in some cases of rheumatic fever, which rises to normal with subsidence of activity. This has been cited as evidence of the occurrence of an antigen-antibody reaction in rheumatic fever. There are several causes for a low serum complement other than fixation by antigen-antibody aggregates. Decreased production of complement is said to occur in liver disease and perhaps in many terminal illnesses. Also, complement levels may be diminished by the presence of inhibitory or anticomplementary substances in the serum. Anticomplementary sera are occasionally found in routine Wassermann tests. The nature of the substances responsible for the inhibition or inactivation of complement is not clear. One such substance may be gamma globulin, a relative preponderance of which causes serum to become anticomplementary.⁵⁵

Predominantly normal or slightly low levels of complement in rheumatic fever were reported by Kellett and Thompson¹³⁶ and more recently by de Gara and Goldberg.⁸⁶ On the other hand, high values during the early period of rheumatic activity were noted by Hadjapoulos and

Burbank in 1928.¹⁰¹ In this respect rheumatic fever did not differ from other febrile illnesses which they studied. The variety of results obtained by different investigators may be attributed in part to the variety of techniques employed and the lack until recently of a reproducible quantitative method for the determination of complement. A satisfactory and reproducible method was described by Mayer, Osler, Bier and Heidelberger in 1946.¹⁷⁹ The 50 per cent hemolytic unit of complement is determined spectrophotometrically in the presence of optimal quantities of magnesium and calcium. Employing this technique fifty cases of active rheumatic fever were studied serially.⁷⁷ Only two showed an initial depression of serum complement, which gradually became normal. In the remaining cases elevated complement levels were found similar to the elevated complement content of sera from various illnesses including pneumonias and penicillin sensitivity. Since there is an elevation of complement in certain allergies studied, the high complement content of most of the rheumatic sera does not preclude the possibility that rheumatic fever may also be an allergic reaction. However, the presence of an elevated complement level in these sera contradicts the suggestion that the low levels previously reported are experimental evidence of an allergic process.

ATTEMPTS TO ALTER THE REACTION

"Specific" Measures. Specific desensitization or immunization of the host to an offending antigen would make more acceptable the hypothesis that rheumatic fever is the result of an allergic process. However, it is difficult if not impossible to desensitize or immunize to bacterial allergic reactions^{134, 237, 263} and, in instances in which this has been achieved, periods of non-reactivity to injected antigens are only temporary. Furthermore, non-reactivity of the skin may depend on non-specific factors such as vascularity while the basic sensitivity of other tissues remains unaltered. Thus, in the presence of a negative skin

reaction to tuberculin, explants of splenic tissue culture showed sensitivity to tuberculin.¹¹³ Attempts at specific desensitization or immunization of rheumatic subjects with streptococcal antigens have been reported to be of some benefit²⁷⁰ but were abandoned after trial by others.^{47, 249, 281} Active immunization, in order to be possible, would obviously depend upon the characteristics of the particular antigen employed.

Unlike the attempts at desensitization or immunization, avoidance of the suspected antigen appears to have been more beneficial. Chemoprophylaxis against the streptococcus, as discussed previously, has become a valuable instrument in the management of rheumatic fever.^{41, 145, 257}

Non-specific Measures. Many agents have been used in the treatment of rheumatic fever but few have remained as constantly in use as have the salicylates and others of the so-called antirheumatic group of drugs. Salicylates have been employed for many years, usually in dosage approaching the limit of tolerance. Despite the popularity of the salicylates and their dramatic effect on fever and arthralgia, their basic efficacy has been questioned.^{95, 176} In the opinion of many, salicylates do decrease the severity of the disease if administered early and perhaps shorten the course of the illness as well. The mechanism of the action of salicylate has remained obscure despite its widespread use over so long a period of time. Investigators have sought for an action more specific to the rheumatic process than the antipyretic and analgesic properties of salicylates. In relation to immunity, salicylates have been said to impair antibody production.^{119, 212} However, the differences reported were not striking for the techniques employed. The formation of antibodies to typhoid vaccine in rheumatic subjects on salicylate therapy was apparently inhibited¹²¹ as compared with the formation of antibodies in normal subjects not on salicylates, a rather unsatisfactory control group. Salicylates caused diminished inflammation at the site of injection of the typhoid vaccine and this

may also account for differences observed, since in certain instances inflammation appears to augment antibody production.⁸¹ Fischel and LeMay (unpublished) immunized four rabbits with crystalline egg albumin intravenously and administered large doses of salicylate three times daily for four to eight weeks. The amount of specific antibody, as determined by the quantitative precipitin technic,¹¹² was comparable to the amount of antibody in the sera of six animals similarly immunized but not treated with salicylate.

Another hypothesis for the mechanism of action of salicylates that has been suggested is that it interferes with the union of antigen and antibody.³⁹ In the test tube, less precipitin was found between egg albumin and anti-egg albumin in the presence of salicylate. The extent of this inhibition is slight in relation to the degree of error inherent in the quantitative precipitin technic, and salicylates were employed in approximately ten times maximal concentrations achieved *in vivo*. In animals and in humans there appeared to be no inhibition of allergic reactions of the Arthus and bacterial types by salicylates.⁷³

Clinical and experimental data have shown no effect of various antihistamine compounds on rheumatic fever or on experimental necrotizing allergies.^{73,74} However, an unusually potent antihistamine, phenergan, possessing other anti-inflammatory properties was found to inhibit the Arthus reaction.^{10a}

Recently Hench and his co-workers demonstrated that cortisone or adrenocorticotrophic hormone (ACTH) produces a dramatic defervescence of activity in rheumatoid arthritis and rheumatic fever.^{115a} The mechanism of action of these hormones is still obscure but speculation concerning the effect of these hormones on immune mechanisms has been advanced.^{206a} Two of several steps in the development of immunity have been studied. ACTH was found to have no influence as an anamnestic stimulus on the production of antibody⁷⁶ and did not affect the tissue damage resulting from

the union of antigen and antibody *in vivo* in the Arthus and anaphylaxis reactions studied by passive, quantitative methods,^{74, 241a} or in anaphylaxis induced after active immunization.^{149a} However, the efficacy of these hormones in clinical hay fever and asthma, noted incidentally in the course of treatment of rheumatoid arthritis and other conditions, suggests that an effect on immune mechanisms is present, and that this effect may also be one of the modes of action of these hormones in rheumatic diseases.^{206a} The experimental study of this hypothesis should prove intriguing.

SUMMARY

Rheumatic fever occurs in certain predisposed individuals but the incidence in some epidemics, and of subclinical cases, appears to exceed estimates based on genetic studies. There is a definite relationship to a preceding infection with the group A hemolytic streptococcus in the great majority of cases of rheumatic fever adequately studied. However, for many reasons summarized the infection does not appear to play more than an initial role in the rheumatic process; rather, a host reaction or allergy to the infection, as has frequently been suggested, is probably the basis for the development of the disease.

Various kinds of necrotizing allergic reactions are reviewed with reference to the mechanisms initiating them. The Arthus type of reaction is related to a circulating antibody and has its clinical counterpart in serum sickness. It has been used extensively as a pattern for attempts at the experimental production of rheumatic-like lesions. The bacterial allergic reactions are distinguished by having fixed tissue antibodies. They have also been used as patterns for animal experimentation. Other experimental approaches involve the use of isoantibodies (cytotoxic antibodies) and autoantibodies. In the absence of other than morphologic criteria, the specificity of the experimentally induced lesions is not adequately established. They cannot, therefore, be unequivocally identified with the lesions of the rheumatic

state although they suggest by analogy that lesions similar to those seen in rheumatic fever may be induced by various allergens.

Clinical studies are reviewed which attempt to define an allergic process in rheumatic patients. Technics involving the detection of isoprecipitins and autoantibodies do not appear constant or specific in this respect and may reflect the occurrence of biologically false positive Wassermann reactions. In the study of serum complement in rheumatic fever various technics have given variable results. A predominantly high complement level in rheumatic fever was found in a recent study. This does not exclude the occurrence of an allergic reaction of the fixed tissue type because several cases of drug allergy also presented high complement levels. There is, as yet, no clinical test for the detection of an allergic reaction in rheumatic individuals that does not occur in patients recovering from a streptococcal infection or certain other diseases.

Finally certain measures employed in rheumatic fever are reviewed with respect to their effect on antigen-antibody reactions. Specific desensitization with the hemolytic streptococcus has been of doubtful value. Salicylates are usually effective in producing a remission of rheumatic activity. However, they apparently do not act on antibody producing mechanisms or by altering the severity of known allergic reactions. The dramatic effectiveness of cortisone or ACTH in the rheumatic diseases should prove extremely valuable in the future study of the pathogenesis of these diseases. The role of these hormones in immune mechanisms, as well as other processes, has yet to be fully studied.

For their encouragement and criticism the author is sincerely grateful to Drs. A. R. Dochez, E. A. Kabat, C. A. Ragan and B. C. Seegal. Thanks are also expressed to Mrs. A. V. Blich for help in the preparation of the manuscript.

REFERENCES

1. AVELL, R. G. and SCHENCK, H. P. Microscopic observations on the behavior of living blood vessels of the rabbit during the reaction of anaphylaxis. *J. Immunol.*, 34: 195, 1938.
2. VON ALBERTINI, A. and GRUMBACH, A. Die experimentelle Streptokokkeninfektion des Kaninchens in ihren Beziehungen zur Herdinfection. *Ergebn. d. Allg. Path. u. path. Anat.*, 33: 314, 1937.
3. ALTMANN, F. and GERZNER, L. Über die Bedeutung der Tonsillen, bzw. des peritonsillären Gewebe für das Zustandekommen hyperergischer entzündlicher Gewebsveränderungen auf tuberkulöser Basis. *Virchows Arch. f. path. Anat.*, 296: 480, 1935.
4. ANDERSON, H. C., KUNKEL, H. G. and McCARTY, M. Quantitative antistreptokinase studies in patients infected with group A hemolytic streptococci: a comparison with serum antistreptolysin and gamma globulin levels with special reference to the occurrence of rheumatic fever. *J. Clin. Investigation*, 27: 425, 1948.
5. ANDREWS, C. H. and GLOVER, R. E. Spread of infection from the respiratory tract of the ferret. I. Transmission of influenza A virus. *Brit. J. Exper. Path.*, 22: 91, 1941.
6. ARONSON, J. D. The specific cytotoxic action of tuberculin in tissue culture. *J. Exper. Med.*, 54: 387, 1931.
7. ASCHOFF, L. The rheumatic nodules in the heart. *Ann. Rheumat. Dis.*, 1: 161, 1939.
8. ASCHOFF, L. and TAWARA, S. Die heutige Lehre von den pathologisch-anatomischen Grundlagen der Herzschwäche. Jena, 1906. G. Fischer.
9. BAKER, B. M., THOMAS, C. B. and PENICK, R. M., JR. Experimental carditis. Changes in the myocardium and pericardium of rabbits sensitized to streptococci. *J. Clin. Investigation*, 14: 465, 1935.
10. BAUER, F. C., JR. Reaction of rats following injection of anti-rat-heart immune serum. *Arch. Path.*, 42: 222, 1946.
- 10a. BENACERRAF, B. and FISCHEL, E. E. Effect of phenergan on the Arthus reaction in rabbits. *Proc. Soc. Exper. Biol. & Med.*, 71: 349, 1949.
11. BIRKHAUG, K. E. Rheumatic fever: allergic reactions with a toxin-producing strain of non-methemoglobin-forming streptococcus isolated from rheumatic fever. *J. Infect. Dis.*, 43: 280, 1928.
12. BJØRNEBOE, M., GORMSEN, H. and LUNDQVIST, F. Further experimental studies on the role of the plasma cells as antibody producers. *J. Immunol.*, 55: 121, 1947.
13. BLAND, E. F. Rheumatic fever and rheumatic heart disease in the North African and Mediterranean Theater of Operations, U.S. Army. *Am. Heart J.*, 32: 545, 1946.
14. BLAND, E. F. and JONES, T. D. Clinical observation on the events preceding the appearance of rheumatic fever. *J. Clin. Investigation*, 14: 633, 1935.
15. BRÜNING, R. and SWIFT, H. F. Comparative histologic reactions in cutaneous lesions induced by streptococci in rabbits previously inoculated intracutaneously or intravenously. *Arch. Path.*, 15: 611, 1933.
16. BONVET, P. L. The streptococcal antifibrinolytic test in clinical use. *J. Clin. Investigation*, 19: 65, 1949.

17. BOUGHTON, T. H. Vascular lesions in protein intoxication. *J. Immunol.*, 2: 501, 1917.
18. BRADLEY, W. H. Epidemic acute rheumatism in a public school. *Quart. J. Med.*, 1: 79, 1932.
19. BRODY, H. and SMITH, L. W. The visceral pathology in scarlet fever and related streptococcus infections. *Am. J. Path.*, 12: 373, 1936.
20. BROKMAN, H., BRILL, J. and FRENDEL, J. Komplementablenkung mit Organextrakten von Rheumatikern. *Klin. Wchschr.*, 16: 502, 1937.
21. BRUNN, E. Experimental Investigations in Serum Allergy with Reference to the Etiology of Rheumatic Joint Diseases. London, 1940. Oxford University Press. Also *Virchow's Arch.*, 303: 524, 1939.
22. BURKY, E. L. The production in the rabbit of hypersensitive reactions to lens, rabbit muscle and low ragweed extracts by the action of staphylococcus toxin. *J. Allergy*, 5: 466, 1934.
23. BURNET, F. M. The Production of Antibodies. Melbourne, 1941. Macmillan & Co., Ltd.
24. CANNON, P. R., WALSH, T. E. and MARSHALL, C. E. Acute local anaphylactic inflammation of the lungs. *Am. J. Path.*, 17: 777, 1941.
25. CAVELTI, P. A. Autoantibodies in rheumatic fever. *Proc. Soc. Exper. Biol. & Med.*, 60: 379, 1945.
26. CAVELTI, P. A. Studies on the pathogenesis of rheumatic fever. II. Cardiac lesions produced in rats by means of autoantibodies to heart and connective tissue. *Arch. Path.*, 44: 13, 1947.
27. CHAEDLE, W. B. The Various Manifestations of the Rheumatic State as Exemplified in Childhood and Early Life. London, 1889. Smith, Elder & Co.
28. CHASE, M. W. Inheritance in guinea pigs of the susceptibility to skin sensitization with simple chemical compounds. *J. Exper. Med.*, 73: 711, 1941.
29. CHASE, M. W. The cellular transfer of cutaneous hypersensitivity to tuberculin. *Proc. Soc. Exper. Biol. & Med.*, 59: 134, 1945.
30. CHILD, C. G. Observations on the pathological changes following experimental hypertension produced by constriction of the renal artery. *J. Exper. Med.*, 67: 521, 1938.
31. CHRISTENSEN, L. R. and MACLEOD, C. M. Streptococcal fibrinolysis: a proteolytic reaction due to a serum enzyme activated by streptococcal fibrinolysin. *J. Gen. Physiol.*, 28: 559, 1945.
32. CLARK, E. and KAPLAN, B. I. Endocardial, arterial and other mesenchymal alterations associated with serum disease in man. *Arch. Path.*, 24: 458, 1937.
33. CLAWSON, B. J. The Aschoff nodule. *Arch. Path.*, 8: 664, 1929.
34. CLAWSON, B. J. Experimental streptococcal inflammation in normal, immune and hypersensitive animals. *Arch. Path.*, 9: 1141, 1930.
35. CLAWSON, B. J. Experimental endocarditis (rheumatic-like and bacterial) in rats. *Arch. Path.*, 40: 153, 1945.
36. COBURN, A. F. The Factor of Infection in the Rheumatic State. Baltimore, 1931. Williams and Wilkins.
37. COBURN, A. F. Observations on the mechanism of rheumatic fever. *Lancet*, 2: 1025, 1936.
38. COBURN, A. F. The prevention of respiratory tract bacterial infections. *J. A. M. A.*, 126: 88, 1944.
39. COBURN, A. F. and KAPP, E. M. The effect of salicylates on the precipitation of antigen with antibody. *J. Exper. Med.*, 77: 173, 1943.
40. COBURN, A. F. and MOORE, L. V. Experimental induction of erythema nodosum. *J. Clin. Investigation*, 15: 509, 1936.
41. COBURN, A. F. and MOORE, L. V. The prophylactic use of sulfanilamide in streptococcal respiratory infections, with especial reference to rheumatic fever. *J. Clin. Investigation*, 18: 147, 1939.
42. COBURN, A. F. and MOORE, L. V. Salicylate prophylaxis in rheumatic fever. *J. Pediat.*, 21: 180, 1942.
43. COBURN, A. F. and MOORE, L. V. Nutrition as a conditioning factor in the rheumatic state. *Am. J. Dis. Child.*, 65: 744, 1943.
44. COBURN, A. F. and PAULI, R. H. Observations on the immunological responses of rheumatic subjects to hemolytic streptococcus. *J. Exper. Med.*, 56: 651, 1932.
45. COBURN, A. F. and PAULI, R. H. The significance of the rise in antistreptolysin level in the development of rheumatic activity. *J. Clin. Investigation*, 14: 769, 1935.
46. COBURN, A. F. and PAULI, R. H. Splenectomy in relation to the development of rheumatic activity. *J. Clin. Investigation*, 14: 783, 1935.
47. COBURN, A. F. and PAULI, R. H. Active and passive immunization to hemolytic streptococcus in relation to the rheumatic process. *J. Clin. Investigation*, 14: 763, 1935.
48. COBURN, A. F. and PAULI, R. H. The significance of prolonged streptococcal antibody development in rheumatic fever. *J. Clin. Investigation*, 18: 141, 1939.
49. COBURN, A. F. and PAULI, R. H. A precipitinogen in the serum prior to the onset of acute rheumatism. *J. Exper. Med.*, 69: 143, 1939.
50. COLLINS, D. H. Observations on the pathology of acute rheumatism and rheumatoid arthritis. *Ann. Rheumat. Dis.*, 1: 38, 1939.
51. COLLINS, W. R. F. Acute rheumatism and hemolytic streptococci. *Lancet*, 1: 1341, 1931.
52. COSS, J. A., JR. Unpublished.
53. DAVIDOFF, L. M., SEEHAL, B. C. and SEEHAL, D. The Arthus phenomenon. Local anaphylactic inflammation in the rabbit brain. *J. Exper. Med.*, 55: 163, 1932.
54. DAVIS, D. Biologic false positive serologic tests for syphilis. *Medicine*, 23: 359, 1944.
55. DAVIS, B. D., KABAT, E. A., HARRIS, A. and MOORE, D. H. The anticomplementary activity of serum gamma globulin. *J. Immunol.*, 49: 223, 1944.
56. DIENES, L. The participation of cutaneous epithelium in immunity response. *J. Immunol.*, 24: 253, 1933.
57. DIENES, L. and MALORY, T. B. Histological studies of hypersensitive reactions. *Am. J. Path.*, 8: 689, 1932.
58. DIENES, L. and SCHOENHEIT, E. W. The reproduction of tuberculin hypersensitiveness in guinea pigs with various protein substances. *Am. Rev. Tuberc.*, 20: 92, 1929.

52. DITKOWSKY, S. P., STEVENSON, E. and CAMPBELL, J. M. An epidemic of rheumatic fever in a children's institution. *J. A. M. A.*, 121: 991, 1943.
53. DOGUEZ, A. R. Etiology of scarlet fever. *Harvey Lect.*, 20: 151, 1924-25.
54. DOUGHERTY, T. F. and WHITE, A. An evaluation of alterations produced in lymphoid tissue by pituitary-adrenal cortical secretion. *J. Lab. & Clin. Med.*, 37: 584, 1947.
55. DRAPER, G. and SEEGAL, D. The importance to the clinicians of the study of genetics. Genetic survey of 50 families with acute rheumatic fever. *Eugenic News*, p. 62, July, 1923.
56. EAGLES, G. H. and BRADLEY, W. H. Agglutination of suspensions of virus-like particles prepared from exudates in acute rheumatic fever. *Quart. J. Med.*, 8: 173, 1939.
57. EAGLES, G. H., EVANS, P. R., KEITH, J. D. and FISHER, A. G. T. Infection experiments with virus-like bodies from rheumatism. *J. Path. & Bact.*, 46: 481, 1938.
58. EATON, M. D., MURPHY, W. D. and HANFORD, V. L. Heterogeneous antibodies in acute hepatitis. *J. Exper. Med.*, 79: 539, 1944.
59. EHRICH, W. L. and HARRIS, T. N. Formation of antibodies in the popliteal lymph node in rabbits. *J. Exper. Med.*, 76: 335, 1942.
60. EHRICH, J. C. and LAPAN, B. The Anitschkow "myocyte." *Arch. Path.*, 28: 361, 1939.
61. EPPINGER, H., FAITSCHKE, J., KAUNITZ, H. and POPPER, H. Über seröse Entzündung. *Klin. Wochenschr.*, 13: 1105, 1137, 1935.
62. ESCHERICH, T. and SCHICK, B. Der Scharlach. Wien, 1912. Hölder.
63. FARLE, H. K. Experimental arthritis in the rabbit; contribution to the pathogeny of arthritis in rheumatic fever. *J. Exper. Med.*, 22: 615, 1915.
64. FAVOUR, C. B. Lytic effect of bacterial products on lymphocytes of tuberculous animals. *Proc. Soc. Exper. Biol. & Med.*, 65: 269, 1947.
65. FLEISMAN, W. H. and FRENCH, C. P. Histologic feature of the intradermic reaction to tuberculin in cattle. *Arch. Path.*, 22: 495, 1936.
66. FISCHL, E. E. Effect of salicylate and tripeleannamine hydrochloride (pyribenzamine) on the Arthus reaction and on bacterial allergic reactions. *Proc. Soc. Exper. Biol. & Med.*, 66: 537, 1947.
67. FISCHL, E. E. Unpublished.
68. FISCHL, E. E. and KAPAT, E. A. A quantitative study of the Arthus phenomenon induced passively in the rabbit. *J. Immunol.*, 55: 337, 1947.
69. FISCHL, E. E., LE MAY, M. and KAPAT, E. A. The effect of adrenocorticotrophic hormone and x-ray on the amount of circulating antibody. *J. Immunol.*, 61: 89, 1949.
70. FISCHL, E. E. and PASTEL, R. H. Serological studies in rheumatic fever. I. The "phase" reaction and the detection of autoantibodies in the rheumatic state. *J. Exper. Med.*, 87: 669, 1949. II. Serum complement in rheumatic fever. *J. Clin. Immunol.*, 25: 1172, 1949.
71. FISCHL, E. and KAPAT, E. A. D-experimentelle lymphogene allergische Arterienverengung. Appendix. *Deutsche Arch. f. path. Anat.*, 217: 146, 1936.
72. FISCUL, J. Beitrage zur Histologie des Scharlachniere. *Ztschr. f. Heill.*, 4: 1, 1883.
73. FRANCISCO, R. Rheumatic heart disease in the tropics with special reference to its incidence in Puerto Rico. *Clinics*, 5: 971, 1946.
74. FREUND, J. and McDERMOTT, K. Sensitization to horse serum by means of adjuvants. *Proc. Soc. Exper. Biol. & Med.*, 49: 548, 1942.
75. FRIED, B. M. Allergic inflammation of the lungs: pathogenesis of lobar pneumonia. *Arch. Path.*, 18: 865, 1934.
76. FRIEDBERGER. Über aseptisch erzeugte Gelenkschwellungen beim Kaninchen. *Berl. klin. Wochenschr.*, 50: 88, 1913.
77. FRIEDBERGER, E. and HARTOGH, O. Über das Verhalten des Komplements bei der aktiven und passiven Anaphylaxie. *Ztschr. f. Immunitätsf.*, 3: 581, 1909.
78. FURTH, J. and KABAT, E. A. Association of the Wassermann antigen with heavy material present in tissue. *Science*, 94: 46, 1941.
79. DEGARA, P. F. and GOLDBERG, H. P. Immunologic and biochemical studies in infants and children with special reference to rheumatic fever. III. Complement titers in abnormal conditions. *Pediatrics*, 2: 248, 1948.
80. GAY, F. P. Tissue resistance and immunity. *Harvey Lect.*, 26: 162, 1930-31.
81. GAY, F. P. et al. Agents of Disease and Host Resistance. Springfield, 1935. Charles C. Thomas.
82. GAY, F. P. and CLARK, A. R. Reticuloendothelial system in relation to antibody formation. *J. A. M. A.*, 83: 1296, 1924.
83. GERLACH. Neue Versuche über hyperergische Entzündung. *Verhandl. d. deutsch. path. Gesellsch.*, 20: 272, 1925.
84. GIBSON, H. J., THOMSON, W. A. R. and STEWART, D. The hemolytic streptococcus as a factor in the causation of acute rheumatism. *Arch. Dis. Childhood*, 8: 57, 1933.
85. VON GLAUN, W. C. Pathology of rheumatism. *Am. J. Med.*, 2: 76, 1947.
86. GLOVER, J. A. and GRIFFITH, F. Acute tonsillitis and some of its sequels: epidemiological and bacteriological observations. *Brit. M. J.*, 2: 521, 1931.
87. GOLDF, W. The hemolytic streptococcus in the aetiology of rheumatic fever and rheumatoid arthritis. *Lancet*, 2: 246, 1938.
88. GRAFF, I., PARENT, S., ZITRON, W. and WYCKOFF, J. Studies in rheumatic fever. I. The natural course of acute manifestations uninfluenced by "specific" therapy. *Am. J. M. Sc.*, 185: 197, 1933.
89. GREEN, C. A. Observations on antistreptolysin O titer in relation to mechanism of acute rheumatic fever. *J. Path. & Bact.*, 53: 223, 1941.
90. GREGORY, J. E. and RICH, A. R. The experimental production of anaphylactic pulmonary lesions with the basic characteristics of rheumatic pneumonitis. *Bull. Johns Hopkins Hosp.*, 78: 1, 1946.
91. GROSS, L. and EHRICH, J. C. Studies on the myocardial Aschoff body. *Am. J. Path.*, 10: 467 and 469, 1934.
92. GROSS, L., LEWIS, L. and ELIASOFF, B. Attempts to produce rheumatic fever in animals. *J. Exper. Med.*, 50: 41, 1929.
93. HADFIELD, G., MAGGE, V. and PERRY, C. B. The

- lysis of fibrin by streptococci: its application to the problems of rheumatic infection in children. *Lancet*, 1: 834, 1934.
101. HADJOPOULOS, L. G. and BURBANK, R. The role of complement in health and disease. A clinical study of the hemolytic complement of human sera. *J. Lab. & Clin. Med.*, 14: 131, 1928.
 102. HALL, E. M. and ANDERSON, L. R. The incidence of rheumatic stigmas in hearts which are usually considered non-rheumatic. *Am. Heart J.*, 25: 64, 1943.
 103. HAMILTON, B. E. and THOMSON, K. J. *The Heart in Pregnancy and the Childbearing Age*. Boston, 1941. Little, Brown & Co.
 104. HANKS, J. H. The mechanism of tuberculin hypersensitivity. *J. Immunol.*, 28: 105, 1935.
 105. HARDGROVE, M., WHITTIER, L. and SMITH, E. R. Rheumatic fever on the Isthmus of Panama. *J. A. M. A.*, 130: 488, 1946.
 106. HARRIS, T. N. Studies on the relation of the hemolytic streptococcus to rheumatic fever. III. Complement fixation versus streptococcal nucleoproteins with sera of patients with rheumatic fever. *J. Exper. Med.*, 87: 57, 1948.
 107. HART, F. D. Rheumatic subcutaneous nodule formation. *Ann. Rheumat. Dis.*, 1: 196, 1939.
 108. HARTLEY, G., JR. and LUSHBAUGH, C. C. Experimental allergic focal necrosis of the liver. *Am. J. Path.*, 18: 323, 1942.
 109. HARTZ, P. H. and VAN DER SAR, A. Occurrence of rheumatic carditis in native population of Curacao, Netherlands West Indies. *Arch. Path.*, 41: 32, 1946.
 110. HAWKING, F. Latent acute rheumatic carditis as determined at autopsy. *Arch. Int. Med.*, 54: 799, 1934.
 111. HAWN, C. VAN Z. and JANEWAY, C. A. Histological and serological sequences in experimental hypersensitivity. *J. Exper. Med.*, 85: 571, 1947.
 112. HEIDELBERGER, M. and KENDALL, F. E. A quantitative theory of the precipitin reaction. III. The reaction between crystalline egg albumin and its homologous antibody. *J. Exper. Med.*, 62: 697, 1935.
 113. HEILMAN, D. H. and FELDMAN, W. H. Specific cytotoxic action of tuberculin. Studies on tissue of tuberculous rabbits in which negative cutaneous reactions to tuberculin have developed. *Am. Rev. Tuberc.*, 54: 312, 1946.
 114. HELPERN, M. and TRUBEK, M. Necrotizing arteritis and subacute glomerulonephritis in gonococcal endocarditis. *Arch. Path.*, 15: 35, 1933.
 115. HENCH, P. S. et al. Rheumatism and arthritis. Ninth rheumatism review. *Ann. Int. Med.*, 28: 66 and 309, 1948.
 - 115a. HENCH, P. S., KENDALL, E. C., SLOCUMB, C. H. and POLLEY, H. F. The effects of a hormone of the adrenal cortex (compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis. Preliminary report. *Proc. Staff Meet., Mayo Clin.*, 24: 181, 1949.
 116. HERRY. Contribution a l'étude du rhumatisme articulaire aigu; essai de pathogénie et de sérothérapie; étude clinique, anatomique et expérimentale. *Bull. Acad. roy. de méd. de Belgique*, 28: 76, 1914.
 117. HITCHCOCK, C. H., CAMERO, A. R. and SWIFT, H. F. Prerivascular reactions in lung and liver following intravenous injection of streptococci into previously sensitized animals. *J. Exper. Med.*, 59: 283, 1934.
 118. HOLBROOK, W. P. The Army Air Forces rheumatic fever control program. *J. A. M. A.*, 126: 84, 1944.
 119. HOMBURGER, F. Sodium salicylate inhibiting anti-Rh immunization in animals. *Proc. Soc. Exper. Biol. & Med.*, 61: 101, 1945.
 120. HOWE, H. A. and BODIAN, D. Second attacks of poliomyelitis. An experimental study. *J. Exper. Med.*, 74: 145, 1941.
 121. HUEPER, W. C. and LANDSBERG, J. W. Experimental studies in cardiovascular pathology. I. Pathologic changes in the organs of rats produced by chronic nitrite poisoning. *Arch. Path.*, 29: 633, 1940.
 122. HUMPHREY, J. H. Antigenic properties of hyaluronic acid. *Biochem. J.*, 37: 460, 1943.
 123. HYDE, R. R. Complement interference—a new explanation for the Neisser-Wechsberg phenomenon. *Am. J. Hyg.*, 8: 730, 1928.
 124. JAGER, B. V. and NICKERSON, M. The altered response of human beings to the intramuscular administration of typhoid vaccine during massive salicylate therapy. *Am. J. Med.*, 3: 408, 1947.
 125. JENNINGS, G. Streptococcus surveys. News letter. Army Air Forces Rheumatic Fever Control Program. 1944–45.
 126. JOKL, E. and MELZER, L. Rheumatic fever following athletic trauma. *Acta med. orient.*, 6: 9, 1947.
 127. JONES, L. and FLEISCHER, M. S. The relation of serum protein fractions to serum sickness in rabbits. *J. Immunol.*, 26: 455, 1934.
 128. KABAT, E. A. The immunochemistry of the proteins. *J. Immunol.*, 47: 513, 1943.
 129. KABAT, E. A. Quantitative immunochemical aspects of some allergic reactions. *Am. J. Med.*, 3: 535, 1947.
 130. KABAT, E. A., MOORE, D. H. and LANDOW, H. An electrophoretic study of the protein components in cerebrospinal fluid and their relationship to the serum proteins. *J. Clin. Investigation*, 21: 571, 1942.
 131. KABAT, E. A., WOLF, A. and BEZAR, A. E. The rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injection of heterologous and homologous brain tissue with adjuvants. *J. Exper. Med.*, 85: 117, 1947.
 132. KALBAK, K. Splenectomy som aktwerende factor ved gigifeber. *Nord. med. (Hospitalstudende)*, 25: 427, 1945.
 133. KALBAK, K. Hemolytic streptococci as an aetiological factor in rheumatic fever and rheumatoid arthritis. Programme, 1st European Rheumatology Congress, Copenhagen, 1947.
 134. KEEFER, C. S., MYERS, W. K. and OPPEL, T. W. Streptococcal agglutinins in patients with rheumatoid (atrophic) arthritis and acute rheumatic fever. *J. Clin. Investigation*, 12: 267, 1933.
 135. KEIL, H. The rheumatic subcutaneous nodules and simulating lesions. *Medicine*, 17: 261, 1938.
 136. KELLET, C. E. and THOMSON, J. G. Complementary activity of blood serum in nephritis. *J. Path. & Bact.*, 48: 519, 1939.

137. KENDALL, J. E., HIDEFERGER, M. and DAWSON, M. H. A serologically inactive polysaccharide elaborated by mucoid strains of group A hemolytic streptococcus *J. Biol. Chem.*, 118 61, 1937.
138. KING, J. G. and FRIDWALD, W. F. Natural antibody that reacts in vitro with sedimentable constituent of normal tissue cells *J. Exper. Med.*, 76 543, 1942
139. KLEMMER, P. The pathogenesis of lupus erythematosus and allied conditions *Arch. Int. Med.*, 28 1, 1948
140. KRIEGL, I. Die Flüssigkeitsüberempfindlichkeit (Gewebelinaphylaxie) der Gelenke *Beitr. z. path. Anat. u. z. allg. Path.*, 83, 185, 1929
141. KRIEGL, I. Der Rheumatismus München, 1933. J. I. Bergmann
142. KLOTZ, O. Arterial lesions associated with rheumatic fever *J. Path. & Bact.*, 18 259, 1913
143. KLOTZ, O. Periarthritis nodosa *J. M. Research*, 37 1, 1917
144. KUCZYNSKI, M. H. and WOLFE Beitrag zur Pathologie der experimentellen Streptokokkeninfektion der Maus (Milz, Leber, Herz) *Verhandl. d. Deutsch. path. Gesellsch.*, 18 47, 1921
145. KUTTNER, A. G. and RIVERSHAULT, G. The prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by the prophylactic use of sulfanilamide *J. Clin. Investigation*, 22 77, 1943
146. KUTTNER, A. G. and KREWMER, F. Observations on the effect of streptococcal upper respiratory infections on rheumatic children—a three-year study *J. Clin. Investigation*, 20 273, 1941
147. LANDSTEINER, R. C. Specific relationship of cell composition to biological activity of hemolytic streptococci *Herz. Let.*, 36 251, 1940 41
148. LANDSTEINER, K. The Specificity of Serological Reactions Cambridge, 1946 Harvard Univ. Press
149. LANDSTEINER, K. and CITANI, M. W. Experiments on the transfer of cutaneous sensitivity to simple compounds *Proc. S. Exper. Biol. & Med.*, 49 488, 1942
150. LECH, J., LEHR, W. and ROSE, B. Effect of adrenocorticotrophic hormone on anaphylaxis *Proc. S. Exper. Biol. & Med.*, 48 148, 1945
151. LEHR, R. and STINE, G. Visceral anaphylaxis after simple subcutaneous injection *Proc. S. Exper. Biol. & Med.*, 51 189, 1944
152. LEHR, W. D. and WHITE, P. D. Anaphylaxis in men due to a mixture of the two because of the *J. I. M. I.*, 84 1545, 1925
153. LONGCOPE, W. T. Effect of repeated injections of foreign protein on the heart muscle. *Arch. Int. Med.*, 15 1079, 1915.
154. LONGCOPE, W. T. Serum sickness and analogous reactions from certain drugs, particularly the sulfonamides *Medicine*, 22 251, 1943
155. LONGCOPE, W. T. and RACKFARN, F. M. The relation of circulating antibodies to serum disease *J. Exper. Med.*, 27 341, 1918
156. LUCIC, H. Uveal tissue sensitization in rabbits by synergic action of staphylococci *Proc. Soc. Exper. Biol. & Med.*, 40, 273, 1939.
157. LURIE, M. B. Heredity, constitution and tuberculosis. An experimental study. *Am. Rev. Tuberc.*, supp 3, vol. 46, Sept., 1941.
158. LURIE, M. B. Studies on the mechanism of immunity in tuberculosis. The fate of tubercle bacilli ingested by mononuclear phagocytes derived from normal and immunized animals *J. Exper. Med.*, 75 247, 1942
159. LYTTEL, J. The Addis sediment count in scarlet fever *J. Clin. Investigation*, 12 95, 1933
160. MCBROOM, J., SUTHERLAND, D. A., MOHR, J. R. and JONES, T. D. Effect of acute scurvy on the guinea pig heart *Arch. Path.*, 23 20, 1937.
161. MACCALLUM, W. G. Rheumatism *J. I. M. I.* 84 1545, 1925
162. McEWAN, C. Cytologic studies on rheumatic fever I. Characteristic cell of the rheumatic granuloma *J. Exper. Med.*, 55: 745, 1932.
163. McEWAN, C. Cytologic studies on rheumatic fever II. Cells of rheumatic exudates *J. Clin. Investigation*, 14 190, 1935.
164. McMASTER, P. D. and HUBACK, S. S. Formation of agglutinins within lymph nodes *J. Exper. Med.*, 61 783, 1935
165. MACNEAL, W. J., BRIVINS, A., STAVIN, A. L. and SCANTON, H. Experimental verrucous endocarditis *Science*, 101 415, 1945
166. MACKENZIE, G. M. and HANGER, I. M. Allergic reactions to streptococcus antigens *J. Immunol.*, 13 41, 1927
167. MACKENZIE, G. M. and LIAM, W. H. Relation of antibody and antigen to serum disease susceptibility *J. Exper. Med.*, 33 601, 1921
168. MAGRASI, F. Experimental infectious rheumatism and streptococcal focal infection *Acta rheumatol.*, 5 2, 1933
169. MAINIER, M. M. and AUSTRIDAM, S. D. Oral penicillin in the prophylaxis of recurrent rheumatic fever *J. Pediatrics*, 31 658, 1947
170. MALLOY, G. K. and KUTNER, C. S. Tissue reactions in fatal cases of Streptococcus hemolyticus infection *Arch. Path.*, 32 334, 1941
171. MARTEL, B. I. and JONES, I. D. The effect of sulfanilamide on rheumatic fever and chorea *Acta Paediatr. Scand.*, 218 876, 1935
172. MARTEL, B. I., MOHR, J. R. and JONES, T. D. The artificial induction of subcutaneous nodules in patients with rheumatic fever *J. Clin. Investigation*, 10 125, 1937
173. MATTE, A. M. and ROYAL, A. Treatment of rheumatic fever patients with and without exudates *J. I. M. I.*, 96 1978, 1932
174. MATTE, M. Über die experimentelle Glomerulonephritis durch das spezifische Antiserum gegen *Zeitschr. f. klin. Med.*, 92 420, 1933-34

178. MASUGI, M., MURASAWA, S. and YA SHU. Über das Vorkommen von Aschoffschen Knötchen in Phthisikerherzen. *Virchows Arch. f. path. Anat.*, 299: 426, 1937.
179. MAYER, M. M., OSLER, A. G., BIER, O. G. and HEIDELBERGER, M. The activating effect of magnesium and other cations on the hemolytic function of complement. *J. Exper. Med.*, 84: 535, 1946.
180. Medical Research Council: Social Conditions and Acute Rheumatism. London, 1927. His Majesty's Stationery Office.
181. MENNE, F. R., JONES, O. N. and JONES, N. W. Changes in the myocardium of rabbits from augmenting the heart rate mechanically and from induced hyperthyroidism. *Arch. Path.*, 17: 333, 1934.
182. METZ, W. Die geweblichen Reaktionserscheinungen an der Gefäßwand bei hyperergischen Zuständen und deren Beziehungen zur Periarthritis nodosa. *Beitr. z. path. Anat. u. z. allg. Path.*, 88: 17, 1932.
183. MEYER, K. The biological significance of hyaluronic acid and hyaluronidase. *Physiol. Rev.*, 27: 335, 1947.
184. MIGOUNOV, B. I. Sur le phénomène intravasculaire de la réaction hyperergique. *Acta Rheumatol.*, no. 23, p. 9, 1934.
185. MILLER, C. P., JR. Spontaneous interstitial myocarditis in rabbits. *J. Exper. Med.*, 40: 543, 1924.
186. MIRSKY, I. A. Artificial induction of subcutaneous nodules in rheumatic fever. *Proc. Soc. Exper. Biol. & Med.*, 60: 143, 1945.
187. MOEN, J. K. Tissue culture studies on bacterial hypersensitivity. II. Reactions of tissues from guinea pigs infected with group A hemolytic streptococci. *J. Exper. Med.*, 64: 355, 1936.
188. MOEN, J. K. and SWIRT, H. F. Tissue culture studies on bacterial hypersensitivity. *J. Exper. Med.*, 64: 339, 1936.
189. MORGAN, I. M. Allergic encephalomyelitis in monkeys in response to injection of normal monkey nervous tissue. *J. Exper. Med.*, 85: 131, 1947.
190. MORGAN, I. M. The role of antibody in experimental poliomyelitis. III. Distribution of antibody in and out of the central nervous system in paralyzed monkeys. *Am. J. Hyg.*, 45: 390, 1947.
191. MOTE, J. R. and JONES, T. D. Studies of hemolytic streptococcal antibodies in control groups, rheumatic fever and rheumatoid arthritis. *J. Immunol.*, 41: 35, 1941.
192. MYERS, W. K., KEEFER, C. S. and HOLMES, W. F. The resistance to fibrinolytic activity of the hemolytic streptococcus with special reference to patients with rheumatic fever and rheumatoid (atrophic) arthritis. *J. Clin. Investigation*, 14: 119, 1935.
193. NEDZEL, A. J. Experimental endocarditis. I. Endothelial changes due to pressor episodes. *Arch. Path.*, 24: 143, 1937.
194. NYE, R. and PARKER, F., JR. Tissue reactions in rabbits following intravenous injection of bacteria. *Am. J. Path.*, 6: 381, 1930.
195. OELLER, H. Experimentelle Studien zur pathologischen Physiologie des Mesenchyms und seiner Stoffwechselleistungen bei Infektionen. *Krankheitsforschung*, 1: 28, 1925.
196. OPIE, E. L. Pathogenesis of the specific inflammatory reaction of immunized animals (Arthus phenomenon). The relation of local "sensitization" to immunity. *J. Immunol.*, 9: 259, 1924.
197. OPIE, E. L. The significance of allergy in disease. *Medicine*, 15: 489, 1936.
198. PAPPENHEIMER, A. M. and VON GLAHN, W. C. Studies in the pathology of rheumatic fever. *Am. J. Path.*, 3: 583, 1927.
199. PAUL, J. R. The Epidemiology of Rheumatic Fever. 2nd ed. New York, 1943. The Metropolitan Life Insurance Co.
200. PEARCE, J. M. Cardiac lesions in rabbits produced by a filterable virus (Virus III). *Arch. Path.*, 28: 827, 1939.
201. PECK, J. L. and THOMAS, L. Failure to produce lesions or auto-antibodies in rabbits by injecting tissue extracts, streptococci and adjuvants. *Proc. Soc. Exper. Biol. & Med.*, 69: 451, 1948.
202. PEMBERTON, R., EIMAN, J., PATTERSON, F. M. S. and STACKHOUS, E. A. Attempts at the experimental production of arthritis. *J. Lab. & Clin. Med.*, 32: 1121, 1947.
203. PENNA DE AZEVEDO, A. Incidencia do reumatismo no Rio de Janeiro. *Mem. Inst. Oswaldo Cruz*, 42: 177, 1945.
204. VON PIRQUET, C. and SCHICK, B. Die Serumkrankheit. Leipzig, 1905.
205. POYNTON, F. J. and PAINE, A. Researches on Rheumatism. London, 1913. J. A. Churchill, Ltd.
206. RACHMILEWITZ, M. and SILBERSTEIN, W. The amount of complement in the blood in rheumatic fever and rheumatoid arthritis. *J. Lab. & Clin. Med.*, 22: 1240, 1937.
- 206a. RAGAN, C., GROKOST, A., and BOOTS, R. H. Effect of adrenocorticotrophic hormone (ACTH) on rheumatoid arthritis. *Am. J. Med.*, 7: 741, 1949.
207. RANTZ, L. A., BOISVERT, P. J. and SPINK, W. W. Etiology and pathogenesis of rheumatic fever. *Arch. Int. Med.*, 76: 131, 1945.
208. RANTZ, L. A. and RANDALL, E. Antibacterial precipitating antibodies in group A hemolytic streptococcus sore throat. *Am. J. Med.*, 2: 551, 1947.
209. RANTZ, L. A., SPINK, W. W. and BOISVERT, P. J. Abnormalities of the electrocardiogram following hemolytic streptococcus sore throat. *Arch. Int. Med.*, 77: 66, 1946.
210. REVENNA, P. Review of recent Italian work on rheumatism. *Ann. Rheum. Dis.*, 1: 167, 1939.
211. VAN RAVENSWAAY, A. C. The geographic distribution of hemolytic streptococci. *J. A. M. A.*, 126: 486, 1944.
212. READ, F. E. M., CIOCCO, A. and TAUSSIG, H. B. The frequency of rheumatic manifestations among the siblings, parents, uncles, aunts and grandparents of rheumatic and control patients. *Am. J. Hyg.*, 27: 719, 1938.
213. REYERSBACH, G., LENERT, T. F. and KUTTNER, A. G. An epidemic of influenza B occurring in a group of rheumatic children concurrent with an outbreak of streptococcal pharyngitis: clinical and epidemiological observations. *J. Clin. Investigation*, 20: 289, 1941.

214. RICH, A. R. Hypersensitivity in disease. *Harvey Lect.*, 42: 106, 1946-47.
215. RICH, A. R. and FORTIS, R. H., JR. Studies on the site of sensitivity in the Arthus phenomenon. *Bull. Johns Hopkins Hosp.*, 66: 106, 1940.
216. RICH, A. R. and GREGORY, J. E. Experimental evidence that lesions with basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. *Bull. Johns Hopkins Hosp.*, 73: 239, 1943.
217. RICH, A. R. and LEWIS, M. R. Mechanism of allergy in tuberculosis. *Proc. Soc. Exper. Biol. & Med.*, 25: 296, 1927-28 and *Bull. Johns Hopkins Hosp.*, 50: 115, 1932.
218. RINHART, J. F., GREENBERG, L. D., O'NEVY, M. B. and CHOY, F. Metabolism of vitamin C in rheumatic fever. *Arch. Int. Med.*, 61: 552, 1938.
219. RINHART, J. F. and METTIER, S. R. The heart valves and muscle in experimental scurvy with superimposed infection, with notes on the similarity of the lesions to those of rheumatic fever. *Am. J. Path.*, 10: 61, 1934.
220. ROSSIT, R. Die morphologischen Aequivalente der Allergie. *Acta rheumatol.*, 8: 64, 1936.
- 220a. ROTHARD, S., WATSON, R. F., SWIFT, H. F. and WILSON, A. In press.
221. RUTSTEIN, D. D. and WALKER, W. H. Complement activity in pneumonia. *J. Clin. Investigation*, 21: 347, 1942.
222. SAIN, A. B. Experimental proliferative arthritis in mice produced by filterable, pleuropneumonia-like microorganisms. *Science*, 89: 228, 1939.
223. SAIN, F. R. Cellular reactions to tuberculo-proteins compared with reactions to tuberculo-lipids. *J. Exper. Med.*, 68: 837, 1938.
224. SCHLESINGER, G. Relationship of throat infection to acute rheumatism in childhood. *Arch. Dis Child.*, 5: 411, 1930.
225. SCHLESINGER, B., SIGNY, A. G., AMIS, C. R. and BARNARD, J. L. Aetiology of acute rheumatism. Experimental evidence of a virus as the causal agent. *Lancet*, 1: 1145, 1935.
226. SCHULTZ, M. P. Cardiovascular and arthritic lesions in guinea pigs with chronic scurvy and hemolytic streptococcal infections. *Arch. Path.*, 21: 472, 1934.
227. SCHULTZ, M. P. Allergic irritability in rheumatic and nephritic patients. *Proc. Helv. Ref.*, 54: 1273, 1939.
228. SCHWENKEL, I. F. and COMPTON, I. C. Production of kidney antibodies by injection of homologous kidney plus bacterial toxins. *J. Exper. Med.*, 70: 223, 1933.
229. STANTON, C. A. The virulence of group C hemolytic streptococci of animal origin. *J. Exper. Med.*, 70: 351, 1937.
230. SIEGAL, B. C. Anaphylaxis. Chapt. 6. Gay and Associates, 1935.
231. SIEGAL, B. C. and LOFF, I. N. The production of chronic glomerulonephritis in rats by the injection of rabbit anti-rat-plasma serum. *J. Exper. Med.*, 84: 211, 1924.
232. SIEGAL, D., HEIDELBERGER, M., JOST, E. L. and LAYNE, J. D. Precipitation and fractions of streptococcal antigen-streptococcal disease, glomerulonephritis, rheumatic arthritis and *S. viridans* endocarditis. *Proc. Soc. Exper. Biol. & Med.*, 30: 582, 1933.
233. SIEGAL, D., HEIDELBERGER, M. and JOST, E. L. The formation of precipitin for the group A specific carbohydrate of *Streptococcus hemolyticus* in rabbits injected intravenously and subcutaneously. *J. Immunol.*, 27: 211, 1934.
234. SIEGAL, D. and SIEGAL, B. C. Local organ hypersensitiveness. 1. Experimental production in the rabbit eye. *Proc. Soc. Exper. Biol. & Med.*, 27: 390, 1930.
235. SIEGAL, D., SIEGAL, B. C. and JOST, E. L. The Arthus phenomenon. Local anaphylactic inflammation in rabbit pericardium, heart and aorta. *J. Exper. Med.*, 55: 155, 1932.
236. SIEGAL, D., SIEGAL, B. C. and JOST, E. L. A comparative study of the geographic distribution of rheumatic fever, scarlet fever and acute glomerulonephritis in North America. *Am. J. M. Sc.*, 190: 383, 1935.
237. SIEVE, H. The general adaptation syndrome and the diseases of adaptation. *J. Clin. Endocrinol.*, 6: 117, 1946.
238. SIERMAN, W. B. Drug allergy. *Am. J. Med.*, 3: 586, 1947.
239. SIFOMUND, H. Über einige Reaktionen der Gefässwände und des Endokards bei experimentellen und menschlichen Allgemeininfektionen. *Verhandl. d. deutsch. path. Gesellsch.*, 20: 260, 1925.
240. SWANET, J. L. and FARR, L. E. Experimental nephritis in rats induced by injection of anti-kidney serum. *J. Exper. Med.*, 65: 527 and 541, 1937.
241. SMITH, J. C. Observations bearing on the specificity of streptococcus cardioarthritis in rheumatic fever and Sydenham's chorea. *Am. J. M. Sc.*, 175: 638, 1928.
- 241a. STORCK, H. C. Personal communication.
242. SWIFT, H. F. The action of sodium salicylate upon the formation of immune bodies. *J. Exper. Med.*, 36: 735, 1922.
243. SWIFT, H. F. Pathogenesis of rheumatic fever. *J. Exper. Med.*, 39: 497, 1924.
244. SWIFT, H. F. Rheumatic fever. *J. A. M. A.*, 92: 2071, 1929.
245. SWIFT, H. F. Rheumatic heart diseases. Pathogenesis and etiology in their relation to therapy and prophylaxis. *Medicine*, 19: 417, 1940.
- 245a. SWIFT, H. F. The etiology of rheumatic fever. Thirtieth annual session. Am. College of Physicians. New York, April 1, 1949.
246. SWIFT, H. F. and BROWN, T. M. Pathogenic, pleuropneumonia-like microorganisms from acute rheumatic exudates and tissues. *Science*, 89: 271, 1939.
247. SWIFT, H. F., DEBICK, C. L. and HITCHCOCK, C. H. Bacterial allergy (hyperergy) to non-hemolytic streptococci in its relation to rheumatic fever. *J. A. M. A.*, 90: 596, 1928.
248. SWIFT, H. F. and HOGEL, B. I. Type-specific anti-M precipitin in rheumatic and nonrheumatic patients with hemolytic streptococcal infections. *Proc. Soc. Exper. Biol. & Med.*, 34: 849, 1936.
249. SWIFT, H. F., HITCHCOCK, C. H., DEBICK, C. L. and McLEWIS, C. Intracranial vaccination with streptococci in rheumatic fever. *Proc. Soc. Exper. Biol. & Med.*, 45: 247, 1930.

250. SWIFT, H. F. and McEWEN, C. Rheumatic Fever. Oxford Medicine. Vol. v, London, 1938. Oxford Univ. Press.
251. SWIFT, H. F., MOEN, J. K. and HIRST, G. K. The action of sulfanilamide in rheumatic fever. *J. A. M. A.*, 110: 426, 1938.
252. SWIFT, H. F. and SCHULTZ, M. P. The synergic action of staphylotoxin and beef lens extract in rabbits. *J. Exper. Med.*, 63: 703, 1936.
253. SWIFT, H. F., WILSON, M. G. and TODD, E. W. Skin reactions of patients with rheumatic fever to toxic filtrates of streptococcus. *Am. J. Dis. Child.*, 37: 98, 1929.
254. TAIALAJEW, W. T. Der akute Rheumatismus. *Klin. Wchnschr.*, 1: 124, 1929.
255. TARAN, L. M., JABLON, J. M. and WEYR, H. N. Cutaneous response to type specific proteins of hemolytic streptococci. *J. Immunol.*, 51: 53, 1945.
256. TARAN, L. M., JABLON, J. M. and WEYR, H. N. Antistreptolysin patterns in rheumatic children. *J. Immunol.*, 53: 381, 1946.
257. THOMAS, C. B. and FRANCE, R. A preliminary report of the prophylactic use of sulfanilamide in patients susceptible to rheumatic fever. *Bull. Johns Hopkins Hosp.*, 64: 67, 1939.
258. THOMPSON, R., GALLARDO, E. and KHORAZO, D. Precipitins in the ocular tissues of rabbits generally and locally immunized with crystalline egg albumin. *Am. J. Ophthalm.*, 19: 852, 1936.
259. THOMSON, S. and GLAZEBROOK, A. J. Infectious diseases in a semi-closed community. *J. Hyg.*, 41: 570, 1941.
260. TILLET, W. S., EDWARDS, L. B. and GARNER, R. L. Fibrinolytic activity of hemolytic streptococci. The development of resistance to fibrinolysis following acute hemolytic streptococcus infections. *J. Clin. Investigation*, 13: 47, 1934.
261. TODD, E. W. Antigenic streptococcal hemolysin. *J. Exper. Med.*, 55: 267, 1932.
262. TODD, E. W., LAURENT, L. J. M. and HILL, N. G. Streptococcal antitoxin and antistreptolysin. *J. Path. & Bact.*, 36: 201, 1933.
263. TODD, E. W., COBURN, A. F. and HILL, A. B. Antistreptolysin S titres in rheumatic fever. *Lancet*, 2: 1213, 1939.
264. TOPLEY and WILSON. Principles of Bacteriology and Immunity. Revised by Wilson, G. S. and Miles, A. A. Baltimore, 1946. Williams & Wilkins Co.
265. TREFFERS, H. P., HEIDELBERGER, M. and FREUND, J. Antiproteins in horse sera. iv. Antibodies to rabbit serum globulin and their interaction with antigen. *J. Exper. Med.*, 86: 95, 1947.
266. TSUDA, S. Experimentelle Untersuchungen über die entzündliche Reaktion der Subcutis in Beziehung zum individuellen Immunitätszustand. *Virchows Arch. f. path. Anat.*, 247: 123, 1923.
267. VAUBEL, E. Die Eiweissüberempfindlichkeit (Gewebshyperergie) des Bindegewebes. *Beitr. z. path. Anat. u. z. allg. Path.*, 89: 374, 1932.
268. VEIL, W. H. and BUCHHOLZ, B. Der Komplementschwund im Blute. *Klin. Wchnschr.*, 11: 2019, 1932.
269. WALSH, T. E., SULLIVAN, F. L. and CANNON, P. R. Local formation of antibody by the nasal mucosa. *Proc. Soc. Exper. Biol. & Med.*, 29: 675, 1932.
270. WASSON, V. P. and BROWN, E. E. Immunization against rheumatic fever. *J. Pediatr.*, 23: 24, 1943.
271. WATSON, R. F., ROTHBARD, S. and SWIFT, H. F. The relationship of postscarlatinal arthritis and carditis to rheumatic fever. *J. A. M. A.*, 128: 1145, 1945.
272. WEDUM, A. G. and WEDUM, B. G. Rheumatic fever in Cincinnati in relation to rentals, crowding, density of population and negroes. *Am. J. Pub. Health*, 34: 1065, 1944.
273. WEDUM, A. G. and WEDUM, B. G. Serum precipitation reaction in rheumatic fever and in other conditions. *Proc. Soc. Exper. Biol. & Med.*, 61: 432, 1946.
274. WEIL, A. J. The Wassermann antigen and related "alcohol-soluble" antigens. *Bact. Rev.*, 5: 293, 1941.
275. WEINTRAUD, W. Ueber die Pathogenese des akuten Gelenkrheumatismus. *Berl. klin. Wchnschr.*, No. 30, 1381, 1913.
276. WESTPHAL, WASSERMANN and MALKOFF. Ueber den infectiösen Charakter und den Zusammenhang von acutem Gelenkrheumatismus und Chorea. *Berl. klin. Wchnschr.*, no. 29, p. 638, 1899.
277. WILENS, S. L., PEARCE, J. M. and FALLAS DIAZ, M. Relative incidence of rheumatic valve disease in New York and Costa Rica and its bearing on the rheumatic origin of calcareous aortic stenosis. *Am. Heart J.*, 30: 573, 1945.
278. WILENS, S. L. and SPROUL, E. E. Spontaneous cardiovascular disease in rats. II. Lesions of the vascular system. *Am. J. Path.*, 14: 201, 1938.
279. WILSON, K. S. and ALEXANDER, H. L. The relation of periarteritis nodosa to bronchial asthma and other forms of human hypersensitiveness. *J. Lab. & Clin. Med.*, 30, 195, 1945.
280. WILSON, M. G. Rheumatic Fever. New York, 1940. The Commonwealth Fund.
281. WILSON, M. G. and SWIFT, H. F. Intravenous vaccination with hemolytic streptococci. *Am. J. Dis. Child.*, 42: 42, 1931.
282. WINBLAD, S. Studies in haemolytic streptococcus fibrinolysin, antifibrinolysin and antistreptolysin (with particular reference to rheumatic fever). *Acta path. et Microbiol. Scandinav.*, Supp. 44, 1941.
283. WU, T. T. Ueber Fibrinoidbildung der Haut nach unspezifischer Gewebsschädigung bei der Ratte. *Virchows. Arch. f. path. Anat.*, 300: 373, 1937.
284. ZINSSER, H. Studies on the tuberculin reaction and on specific hypersensitiveness in bacterial infection. *J. Exper. Med.*, 34: 495, 1921.
285. ZINSSER, H. and ENDERS, J. F. Variations in the susceptibility of guinea pig to reversed passive anaphylaxis. *J. Immunol.*, 30: 327, 1936.
286. ZINSSER, H., ENDERS, J. F. and FOTHERGILL, L. D. Immunity: Principles and Application in Medicine and Public Health. New York, 1939. The Macmillan Co.
287. ZINSSER, H. and GRINNELL, F. B. Further studies on bacterial allergy. Allergic reactions to the hemolytic streptococcus. *J. Immunol.*, 10: 725, 1925.
288. ZUGER, B. Group infection and immunity during a scarlet fever epidemic in a boys' school. *Am. J. Hyg.*, 21: 588, 1935.

Seminars on Antibiotics

Bacitracin*

FRANK L. MELENEY, M.D. and BALBINA A. JOHNSON, B.A.

New York, New York

THE antibiotic, bacitracin, is produced by the Tracey I strain of *Bacillus subtilis* which was discovered in June, 1943, in the Laboratory of Bacteriological Research of the Department of Surgery, College of Physicians and Surgeons, Columbia University.¹ The organism was recovered from the damaged tissue and street dirt débrided from the compound fracture of a seven year old child by the name of Tracey. The antibiotic was therefore named "bacitracin."

PROPERTIES OF THE ORGANISM AND ITS FILTRATE

Dr. Kenneth Burdon of Baylor University has studied the cultural characteristics of this organism and has classified it as a *B. licheniformis* but as far as the authors know, no other strain of this species has been found able to produce this antibiotic. The active principle is secreted into any medium in which the organism will grow but the amount of the antibiotic depends upon the composition of the medium, the condition of the seed cultures and the circumstances of incubation. The organism forms a thick pellicle on the surface of the media but very little active principle can be obtained from this bacterial mass. The active agent is readily obtained in the filtrate of the decanted media after passage through a Chamberland, Berkefeld, Selas or Seitz filter.

Preliminary studies of the filtrate showed that it had a powerful antibiotic action with a wide antibacterial spectrum. (Table I.)

When produced on a glutamic acid synthetic medium, bacitracin showed no toxicity when injected into laboratory animals in fairly large quantities over a long period of time. It was then found to be non-toxic and non-irritating when injected in small quantities into human beings. It was found to be capable of controlling experimental hemolytic streptococcal peritonitis in mice when injected subcutaneously several hours after the intraperitoneal injection of the organisms, thus indicating that it was absorbed and could reach an area of infection some distance away from the site of injection. It was also able to prevent gas gangrene following the intramuscular injection of *Clostridium welchii* in guinea pigs.¹ Furthermore, it was capable of promptly controlling infections such as furuncles, carbuncles and superficial abscesses when injected into the center of such lesions in human beings.

The extraction and partial purification of bacitracin was carried out by Dr. Herbert Anker of the Department of Biochemistry with the advice and counsel of Professor Hans Clarke. These studies were reported by Anker, Johnson, Goldberg and Meloney in 1948.²

CHEMICAL PROPERTIES OF LABORATORY BACITRACIN

The chemical properties of the laboratory product were found to be as follows:

Stability. Partially purified neutral or slightly acid (pH 6.6) aqueous concentrates of bacitracin prepared by the butanol

* From the Laboratory of Bacteriological Research, Department of Surgery, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y. Part of this work was done under a contract between Columbia University and the Office of Scientific Research and Development of the United States and the Medical Research and Development Board of the Surgeon General of the Army, and part was done under grants in aid from the United States Public Health Service.

method showed no detectable change in titer after storage for eight months to one year at temperatures of 0° to 5°C. At room temperature there was a loss of 30 to 50 per cent of the activity after a two weeks' storage period but neutral, inorganic salt-free solutions were dried at room temperature without loss of activity. Inactivation was complete after two weeks at 35° to 37°C. Bacitracin solutions were stable to normal hydrochloric acid at 0° to 5°C and to 0.01 normal hydrochloric acid at both 0° to 5°C and 37°C. They were rapidly inactivated in alkaline solution above pH 9 at both temperatures. In the presence of hydrogen peroxide there was complete loss of antibiotic activity. In 1947 Scudi et al. found that bacitracin was partially inactivated by BAL and sodium thiosulfate.³

Solubility. The laboratory product of bacitracin was found to be soluble in methanol, ethanol, isopropanol, *n*-butanol and cyclohexanol, slightly soluble in cyclohexanone, and insoluble in other organic solvents such as ether, chloroform, benzene, acetone and ethyl acetate. In aqueous solution the activity was diffusible through a nitrocellulose membrane which holds back particles of molecular weight 2,000.

Precipitability. 1. *Metal ions:* Bacitracin was precipitated by salts of heavy metals. This precipitation was accompanied by inactivation if the heavy metal ions, low in the electromotive series, were used. On the other hand, the action of zinc ions, high in the electromotive series, did not result in inactivation but precipitation of the active material was incomplete.

2. *Organic acids:* Several organic acids were found to precipitate the activity from concentrates, namely, trichloroacetic, tannic, azobenzene-*p*-sulfonic, benzoic, furoic and salicylic acids. With the first two, considerable activity disappeared during the isolation of the bacitracin. The results with benzoic acid were variable. Large quantities of furoic acid were required to precipitate the antibiotic and the percentage of recovery was low. Salicylic acid, however, yielded precipitates with all batches

tested; the yields were high and no inactivation was observed.

3. *Other precipitants:* Bacitracin was also precipitated from water solution by high concentrations of sodium chloride, acetone, ammonium rhodanilate, Reinecke's salt and molybdic acid.

Adsorption. Bacitracin was found to be adsorbed on charcoal, Lloyd's reagent and aluminum oxide but the problem of elution had not then been solved.

These preliminary studies clearly indicated the necessity for the further production, purification and clinical appraisal of bacitracin. In order to carry this out it was decided to call upon one of the commercial firms to produce it in large quantity.

COMMERCIAL PRODUCTION OF BACITRACIN

The first attempt to transfer production from laboratory to commercial methods was made by Lederle but difficulties were encountered and most of the antibiotic was lost during the process of extraction. It was then taken over by the Ben Venue Laboratories of Bedford, Ohio. After six months of experimentation a method was found which produced the antibiotic in soybean medium, yielding ten times the assay obtained from the synthetic medium. Furthermore, a shortcut was found in the extraction process by adsorbing the antibiotic on charcoal and eluting it with dilute hydrochloric acid. The original method of growth on the surface of the medium was continued and in the course of a year a stable, lyophilized, slightly yellowish white powder was obtained of sufficient purity to warrant a pharmacologic study.

During the various stages of development the commercial product* steadily increased in purity; even the early crude preparations were effective when applied to infected areas and surfaces. Experiences with the first hundred cases of surgical infections so treated served as the basis for a report by

* The commercial bacitracin used in these studies was supplied by the Ben Venue Laboratories of Bedford, O., and the Commercial Solvents Corporation of Terre Haute, Ind.

the authors which was published in March, 1947.⁴

These cases represented the general run of localized or localizing infections which are seen every day in any surgeon's office or any hospital clinic. Eighty-eight per cent of these patients responded favorably to the drug treatment. Bacteriologic studies revealed that the majority of surgical infections are due to a mixture of organisms. When the organisms associated with these infections were tested for sensitivity to bacitracin and penicillin, most of them were found to be susceptible to both. Thirty were susceptible to bacitracin and resistant to penicillin while only six were resistant to bacitracin and susceptible to penicillin. It was found that the daily aspiration of superficial or even deep abscesses followed by the instillation of bacitracin often caused rapid resolution of the process and often obviated surgical incision. Similarly, the application of a solution or ointment containing bacitracin in a concentration of 500 units per cc. of solution or Gm. of ointment to an infected wound or superficial ulcer often caused rapid disappearance of the infecting organisms and healing of the wound.

PHARMACOLOGIC STUDIES OF BACITRACIN

The pharmacologic studies were under the direction of Dr. John Scudi of the Department of Pharmacology of the College of Physicians and Surgeons, Columbia University, with the advice and counsel of Professor Harry B. van Dyke. These studies served as the basis for three reports which appeared in 1947.^{3,5,6}

Acute toxicity experiments were carried out in Rockland Swiss mice and in Sherman rats. Several different lots of bacitracin were tested and it was found that the toxicity of the different lots varied independently of the activity and that the aforementioned lot was least toxic. It was also noted that inactivation of the material by incubation at 37°C. for eight days at a pH of 7 did not alter the toxicity of the preparation whereas its antibiotic activity was completely lost in

that time. The only injury to any of the organs or tissues of the body was in the lower renal tubules with large doses of the antibiotic. Mice and to a lesser degree monkeys were affected whereas dogs and rats showed no injury to the kidneys. The subcutaneous LD-50 in mice was four to seven times the intraperitoneal LD-50 and lethal results were produced only with immense oral doses.

The absorption and excretion of bacitracin was studied in the dog. Significant concentration of the drug persisted in the blood stream as long as seven or eight hours after parenteral administration. Dogs showed no signs of toxicity even when doses as high as 6,000 units per Kg. of body weight were used, other than slight or transient vaso-depressor effects produced by rapid intravenous injection. Recovery of the drug in the urine showed wide variations but in general it increased in direct ratio to the dose administered. However, significant concentrations of the drug could be found in the urine more than seven hours after the administration of a single dose of the antibiotic. Concentrations of 14 to 18 units per cc. could be found in dogs' urine seven hours after a single intramuscular injection of 1,000 units per Kg. and as high as 92 units per cc. after a 3,000 unit per Kg. dose. These figures for the urinary excretion of bacitracin following intramuscular administration are in sharp contrast to those after oral administration. Scudi could detect no bacitracin in the urine after a single oral dose of 3,000 to 6,000 units per Kg. The highest recovery reported by Bond et al.⁷ after oral administration in the dog was 0.22 units per cc. after the 10,000 unit per Kg. dose, and 1.65 units per cc. after the 20,000-unit per Kg. dose.

Scudi also found that although bacitracin remained in the blood stream for many hours, it did not penetrate the red blood cells nor did it enter the spinal fluid freely. Following prolonged daily administration of crude bacitracin concentrates in dogs and monkeys there were no significant changes in blood morphology.

Concentrations of bacitracin of 6,000 units per cc., when injected into the abdominal skin of experimental rabbits, caused no irritation and there was no reaction to 1,200 units per cc. in the conjunctival sac of rabbits. There was some induration after repeated intramuscular injections into the dog while in the monkey there were at times small areas of necrosis of the muscle at the sites of the injections.

In the dog the urine samples remained negative for sugar and albumin but both of these appeared in the urine of monkeys. Large doses approximating the LD-50 produced some damage to the renal tubules in the mouse and occasionally in the monkey, but the lesions were insignificant in the rat and in the dog. Scudi considered the toxicity to be of the same order as that of streptomycin.

EARLIEST SYSTEMIC ADMINISTRATION OF BACITRACIN

With this preliminary demonstration of relatively low toxicity, it was deemed safe to start cautiously subcutaneous, intramuscular and mouth administration of bacitracin in human volunteers. It was found that blood and urine levels could be obtained by subcutaneous and intramuscular injections, but only urine levels and those of low degree when the drug was given by mouth. We then began cautiously to treat patients with intramuscular injections in gradually increasing doses ranging from 3,000 to 20,000 units every six hours. With all of these doses it was found that detectable blood levels of bacitracin could be found six hours after administration. In the first case of infection treated systemically the administration of 3,000 units every six hours was stopped on the third day when albuminuria appeared, but it promptly disappeared. Later cases with increased dosage showed a transient albuminuria and a few granular casts but these findings disappeared during the course of treatment and there were no clinical signs of toxicity. Furthermore, the infections for which these

patients were treated, in most cases, came promptly under control.

With the same material Dr. Harry Eagle found that bacitracin had a lethal action on spirochetes and that he could cure his experimental rabbits with syphilis by its systemic administration. He also found that bacitracin had a lethal action on spirochetes directly proportional to its concentration, that it was slowly eliminated through the kidneys at the rate of glomerular filtration and that it had a striking synergistic action with penicillin in the cure of experimental syphilis.⁸ Therefore, he started a study of the treatment of human syphilis with bacitracin alone and with bacitracin in combination with penicillin. The report of this study will be published elsewhere.⁹

During this period units were set up in several different cities for the clinical appraisal of bacitracin. These were organized by Dr. Alfred Longacre in New Orleans, Major Edwin J. Pulaski at Fort Sam Houston, Dr. Edward H. Reisner, Jr., at Bellevue Hospital in New York, Dr. Harold Zintel in Philadelphia and Dr. William Altemeier in Cincinnati, beside the unit already in operation at Presbyterian Hospital in New York under the direction of the authors of this paper.

The number of patients treated systemically during the spring, summer and fall of 1947 increased slowly because of the fact that production was delayed, not only in the Ben Venue Laboratories but also in the laboratories of the other manufacturers, all of whom encountered production difficulties. In December, 1947, the Commercial Solvents Corporation began to produce bacitracin by the deep tank method. By an agreement with the Ben Venue Laboratories the whole output and experience of Ben Venue in the production of bacitracin was turned over to the Commercial Solvents Corporation. Thereafter production by the surface growth method was given up and the deep tank method was employed. Bacitracin was produced by the Commercial Solvents Corporation only in small quantities during the months of December, Janu-

ary and February and extensive clinical observations were not made with it until the spring of 1948, inasmuch as it was decided to use up the available Ben Venue material first. The units in Philadelphia and San Antonio, which were started later than the others, had little or no experience with the Ben Venue material and their first patients were treated almost entirely with the Commercial Solvents product.

From August, 1946, to March, 1948, the systemic administration of bacitracin made by the Ben Venue Laboratories by the surface growth method was continued with increasing confidence in its efficacy and safety. The albuminuria and cylindruria had proved to be of a low order and in the majority of cases these signs of kidney irritation disappeared during the course of treatment or promptly after the cessation of treatment. Occasionally intramuscular injection was followed by nausea and in some cases by vomiting but this did not interfere with treatment except in one case, a paraplegic with a chronic decubital ulcer.

However, during this period an effort was made to remove all evidences of toxicity and we were encouraged by the fact that with the ultracentrifuge toxic products could be carried down to the heavy portion of the solution, while bacitracin was evenly distributed.

TENTATIVE F.D.A. SPECIFICATIONS FOR BACITRACIN

In January, 1948, at the request of the Surgeon General's Office, Dr. Henry Welch of the Food and Drug Administration, called a meeting in Washington of the commercial firms interested in the manufacture of bacitracin for the purpose of setting up specifications dealing with potency, solubility, stability, toxicity and pressor, depressor and pyrogenic effects. The most important specifications dealt with potency and toxicity and we recommended that a toxicity specification be set up at an LD-50 of 500 and an LD-0 of 250 units for a 20-G. mouse by intraperitoneal or intravenous injection, but the manufacturers claimed

that this level would be difficult to attain and our clinical experience with the Ben Venue product seemed to indicate that lower figures would give a sufficient margin of safety. Therefore, toxicity levels were set at 200 units for the LD-50 and 100 units for the LD-0, with the understanding that further attempts would be made to raise these standards as the manufacturers improved their product.

FIRST CONFERENCE ON RESULTS OF BACITRACIN TREATMENT

In March, 1948, a meeting was called in New York at the Columbia-Presbyterian Medical Center to which the leaders of the study units and the manufacturers were invited for a full presentation of their experiences with bacitracin both in the laboratory and in the clinic. At that meeting Dr. Lyman Craig of the Rockefeller Institute gave a preliminary report on the purification of bacitracin by his counter-current apparatus. He stated that the commercial product contained three organic substances and one inorganic. One of the organic substances predominated and this was made up of a number of amino acids. Chromatographic studies identified many of these.

By the time of the March meeting the number of surgical infections treated locally had reached 200 and favorable results had been obtained in 87 per cent of these cases. Furthermore, it was found that a fairly large number of the organisms associated with these infections were resistant to penicillin and susceptible to bacitracin. At the same time a large series of cases of dermatologic infections were reported by Dr. J. Lowry Miller.¹⁰ The dermatologists were particularly impressed with the high rate of cure and the low incidence of allergic reactions to bacitracin as contrasted with penicillin and the sulfonamides.

Experiments were carried out with various bases in order to find one that would be more stable than the carbowax propylene glycol base previously used. Such bases were made primarily either with lanette wax or

with cetyl alcohol. These bases readily released the antibiotic and this did not deteriorate as rapidly at room temperature as it did in the carbowax base. In grease bases the bacitracin was still more stable but it was not as readily released from them.

A study of the development of resistance to bacitracin of susceptible bacteria was made during this period and it was found that a few strains slowly developed resistance but this was of a low order and of slow development. In dermatologic and local surgical infections this appeared to be inconsequential because it was easily overcome by the concentration of the antibiotic used with local application.

At the March meeting Dr. Alson Braley of the Department of Ophthalmology stated his belief that bacitracin was the treatment of choice in ophthalmic infections because of its effectiveness and the low incidence of allergic manifestations. Dr. Edward Reisner reported success in the systemic treatment of pneumonia at Bellevue Hospital. Dr. Harry Eagle of Baltimore discussed the preliminary steps in his study of bacitracin in the treatment of syphilis.

For the treatment of systemic infections the units had gathered data which were listed on carefully prepared summary sheets designed to permit the transfer of all important information regarding every case to punch cards for statistical analysis. Up to that time the unit at the Presbyterian Hospital had treated thirty patients with various types of infections and reports from the various units totaled approximately 100 cases of all types, both medical and surgical. All of the units which had been functioning for several months reported gratifying results in the treatment of infections and increasing confidence in the safety of the drug. The evidences of kidney irritation were minimal and transient and they did not interfere with the course of treatment. However, for the first time a disquieting note was struck by Major Pulaski, who noted that a few patients treated with the Commercial Solvents

material made by the deep tank growth of the organism had shown more evidence of kidney damage than the other units had observed, as indicated by larger amounts of albumin in the urine and an increased number of granular casts, renal epithelial cells and red blood cells and higher levels of retained urea nitrogen and non-protein nitrogen in the blood.

BACITRACIN IN AMEBIASIS

During the month of March, 1948, it was reported by Dr. E. C. Faust¹¹ of Tulane University in New Orleans that he had found *Endameba histolytica* susceptible to bacitracin, and because of the striking sensitivity of associated intestinal bacteria of the clostridial and coccal groups, plans were formulated for an intensive study of amebiasis.

This study was carried out by Dr. Harry Most of the Department of Preventive Medicine of New York University.¹² The patients were for the most part returned veterans from World War II who had acquired their infestation in widely separated war areas. Treatment was carried out in New York where re-infestation from outside sources was unlikely. Sixty patients were treated all of whom were having active symptoms and signs of amebiasis. The first fifty patients received bacitracin by mouth in amounts ranging from 40,000 to 160,000 units a day in divided doses for a period of twenty days. A careful follow-up of these cases was carried out over a period of six to twelve months. There were no clinical failures but there was a relapse rate of about 30 per cent, as represented by a return of the *Endameba histolytica* in the stools without any clinical symptoms. These organisms are being studied further to see if they have lost their pathogenicity. Some of the patients with relapses responded to a second series of treatments with a higher dosage. The last ten patients were treated with 160,000 units a day for twenty days. They have not yet been followed long enough to determine the percentage of cures. In all of these patients there were

only two who showed any disturbances from the treatment itself. One of these had a diarrhea for two days and the other a diarrhea for seven days with distention but this did not require cessation of treatment. The drug was only slightly absorbed from the gastrointestinal tract. It was recovered in small quantities in the urine but no blood levels were demonstrable. High concentrations were still present in the stool.

Dr. Alfred Longacre and Dr. D'Antoni obtained similar results in New Orleans.¹³ Their problem of follow-up studies was more difficult because of the possibility of re-infestation from outside sources. Doses as large as 250,000 units a day were given without evidence of toxicity.

BACITRACIN IN NEUROLOGIC INFECTIONS

In the spring of 1948, Dr. Paul Teng, working on the problem of staphylococcic meningitis, demonstrated that bacitracin given intramuscularly in normal dogs can be found in only small quantities in the spinal fluid, indicating difficulty in passing the blood-brain barrier. However, if the meninges are inflamed by the injection of staphylococci into the cisterna magna of dogs, bacitracin enters the spinal fluid in considerably higher concentration. He also demonstrated that if meningitis is produced by the cisternal injection of staphylococci, the animals die within four or five hours of an extensive meningitis; but if bacitracin is instilled into the cisterna magna in such cases, they may be saved even when treatment is initiated two or three hours after inoculation with the bacteria. Furthermore, bacitracin may be injected intrathecally in a concentration of 10,000 units per cc. without showing any signs of irritation of the meninges from the drug.¹⁴

Dr. William Cone in Montreal has recently demonstrated that powdered bacitracin, containing 50 units per mg., may be applied to the surface of the brain without causing the convulsions which are characteristic of the application of penicillin, streptomycin and the sulfonamides. Moreover, it can be injected into the brain tissue

or into the ventricles in a concentration of 1,000 units per cc. without causing any evidence of irritation.

BACITRACIN IN THE TREATMENT OF PNEUMONIA

Reisner continued his study of the intramuscular injection of bacitracin in cases of pneumonia until he had a series of twenty-five.¹⁵ In a preliminary group of eleven cases he found that doses as small as 15,000 units every six hours would cause rapid resolution of the process if the organism had not invaded the blood stream, but that higher doses were necessary in the presence of septicemia. In his second series of fourteen cases the initial treatment was usually 30,000 units every six hours, but in several instances of severe and extensive infection he doubled this dose and in one patient gave as much as 99,000 units every six hours. He recommended the use of bacitracin in cases of pneumonia caused by a sensitive organism which did not respond to penicillin. In his second series there was only one death and that patient had already developed endocarditis when treatment with bacitracin began. The patient failed to respond not only to bacitracin but to penicillin as well. One other patient with a relatively resistant organism failed to respond to bacitracin but was quickly restored by large doses of penicillin. In this series of cases evidences of nephrotoxicity were minimal and none of the patients showed any permanent or serious damage to the kidneys.

NEPHROTOXICITY OF SYSTEMIC BACITRACIN

Up until May, 1948, further observations were made with the systemic administration of bacitracin and these provided data in 105 cases of surgical infections which were reported to the American Surgical Association at the meeting in Quebec. In this report the recent appearance of disturbing nephrotoxicity was discussed.¹⁶

During this period Dr. Alexander Michie at the University of Pennsylvania studied

glomerular and tubular filtration in several patients after the administration of bacitracin in daily doses of 200,000 units for varying numbers of days. He found that both of these excretory functions as well as renal blood flow were temporarily but materially diminished. The renal plasma flow in six patients treated for four to nineteen days was reduced 46 per cent. In these same cases the glomerular filtration was diminished 40 per cent. In five of these patients treated for five to nineteen days the tubular filtration was diminished 61 per cent. These sets of figures, however, did not run parallel with each other nor with the total dosage of the drug. Moreover, later tests showed a return toward normal in every case.¹⁷ These experiments were carried out with two Commercial Solvents' lots of bacitracin and a later review of the clinical results with these lots in all of the centers of observation indicated that they were among the most toxic.

Toward the end of this period more cases showing nephrotoxicity appeared in all of the units which were now beginning to use the Commercial Solvents material made in the deep tanks since most of the surface growth product had been used up. It was then evident that the specifications for toxicity which the Food and Drug Administration had set up were too low and that the problem would require a thorough study.

The summary sheets covering the clinical data from all of the patients previously treated were carefully scrutinized from the point of view of the lot numbers and the dosage used. These items were correlated with the laboratory and clinical evidence of kidney irritation. At the same time six representative lots from both the surface growth and from the deep tank product, all of which had been used clinically, were injected subcutaneously into mice in doses ranging from 250 to 1,000 units. Four hundred eighty-four mice were used in this study. With each lot the death rate was noted and after a period of several days the surviving mice were sacrificed and notes

were made with regard to the evidence of gross renal disorders.

When all of the laboratory and clinical data were analyzed, it was obvious that the early deep tank product was definitely more toxic than the surface growth product. Furthermore, it was evident that different lots of the deep tank product differed from one another in their toxicity. These lots had all been tested for safety by the laboratories of the Food and Drug Administration and it was found that the LD-50 for 20-gram mice ranged all the way from 224 to 500 units. It was then found that these F.D.A. tests corresponded very closely with the clinical and laboratory data mentioned above. The lot which met the LD-50 test of 500 units was by far the least toxic in its clinical record in cases of surgical infections and pneumonia.

When faced with the clinical and laboratory data, the deep tank manufacturers suggested that, inasmuch as their product had a higher assay and was therefore purer than the surface growth product, some inhibiting substance which had reduced the toxicity of the surface growth material might have been removed by their process. It had been demonstrated and repeatedly confirmed that the presence of certain salts materially cuts down the toxicity. It was pointed out that certain of the *d*-amino acids were known to have nephrotoxic action. These might be the responsible elements causing toxicity and their action might be nullified by the presence of the *l*-isomers. It was therefore decided to make a thorough study of the amino acid and salt content of a number of different lots produced by the two methods.

Inasmuch as the surface growth material was almost exhausted, we were dependent entirely upon the Commercial Solvents deep tank bacitracin. Fortunately, other lots made fairly recently met the 500-unit specification and these were selected for further clinical trial. It was agreed that initial doses should approximate 200 units per Kg. of body weight and that these doses should be increased only if the initial dose

failed to control the infection under treatment. This plan was followed during the course of the next eleven months and the favorable results obtained with a minimum of disturbing toxic manifestations amply

justified this program and has restored confidence in the safety and efficacy of the antibiotic.

In order to be certain that the low incidence of nephrotoxic responses in the patients receiving the bacitracin with the LD-50 of 500 was not simply a question of low dosage, six patients during this period were given the same doses from two lots which fell short of this specification. Four of the six gave disturbing signs of toxicity which disappeared as soon as they were taken off this material and given the same dosage with a less toxic lot. One of these patients had been given some of the surface growth bacitracin a year previously for a period of one month in a dosage 50 per cent higher without any evidence of toxicity.

THREE PHASES OF CLINICAL EXPERIENCE WITH BACITRACIN

Thus the clinical experience of the various units which were set up for the clinical appraisal of bacitracin over a period of twenty-two months has had three phases: (1) a period of calm and complacency during which satisfactory results were obtained in about eighty-five cases without toxic manifestations, using the surface growth bacitracin; (2) a period of storm, stress and uncertainty while we treated another eighty-five patients with the early deep tank bacitracin and encountered disturbing evidences of kidney irritation or damage from particularly toxic lots and (3) a period of increasing confidence in the efficacy and safety of bacitracin which meets the specification for toxicity of LD-50 of 500 units for a 20-gram mouse. This has covered about a hundred cases, making a total of 270 for the entire series.¹⁸

FURTHER PURIFICATION STUDIES

In the meanwhile studies have been going on in an effort to purify further the commercial product. Craig, Gregory and Barry¹⁹ have subjected it to their counter-current distribution apparatus and have been able to take material with an initial potency of 46 units per mg. and separate

TABLE I
ANTIBACTERIAL SPECTRUM OF BACITRACIN

Organisms	*Sensitive to Bacitracin (in units)	*Resistant to Bacitracin (in units)
Aerobic Bacteria:		
β hemolytic streptococci		
Groups A, B, C, F, G	0 025-0.005	
Group D	3-0 008	
Non-hemolytic streptococci	3-0 025	
Pneumococci	0 1-0 002	
Staphylococci (coagulase +)	5-0 05	
Other micrococci	5-0 008	
C. aerose	0 005-0 003	
C. diphtheriae	0 015-0 004	
N. meningitidis	0 01	
N. gonorrhoeae	0 006	
†B. anthracis	4-12.5	
B. subtilis group		50
E. coli		50
A. aerogenes		50
A. cloacae		50
Proteus		50
Ps. aeruginosa		50
B. alkaligenes		50
S. typhosa		50
Sh. alcalescens		50
Flavobacterium (New Orleans strain)	0 0025	
†H. influenzae Type B	63	
Anaerobic Bacteria:		
Cl. welchii	0 025-0 002	
Cl. septicum	0 01-0 002	
Cl. sordellii	0 01-0 005	
Cl. novyi	0 01	
Cl. tetani	0 01-0 006	
Cl. histolyticum	0 025-0 004	
Hemolytic streptococci	0 01-0 001	
Non-hemolytic streptococci	0 1-0 005	
Micrococci	0 5-0 005	
Diphtheroids	0 003	
Actinomyces israeli	0 075-0 005	
§T. pallidum (Reiter strain)	0 004	
Fungi:		
Monilia albicans		50
Cryptococcus hominus		50
Nocardia asteroides		50

* Beef heart infusion broth tube assay.

† Occasional strains sensitive 3-0.5 units.

‡ EVANS, F. J. *Bact.*, 56: 507, 1948.

§ EAGLE, H., MUSSELMAN, A. D. and FLEISCHMAN, R. *J. Bact.*, 55: 347, 1948.

from it a single active substance with an assay of 66 units. Hydrolysis of this material in 6 normal hydrochloric acid followed by paper chromatography gave spots corresponding to phenylalanine, leucine, isoleucine, cysteine, valine, histidine, ornithine, lysine and glutamic and aspartic acids. This strongly suggests that the active principle is a polypeptide of considerable size. All of the constituent amino acids indicated by paper chromatography have been isolated in crystalline form with the correct carbon and hydrogen analyses except lysine and ornithine. The amino acids isolated were as follows: *l*-histidine, partially racemic and *l*-leucine, *l*-cysteine and *l*-glutamic acid, *d,l*-phenylalanine, *d,l*-aspartic acid and partially racemic and *d*-isoleucine. One of the purified specimens showed definite organization when examined microscopically.

Further studies in the Biochemistry Laboratory of the College of Physicians and Surgeons by Miss Catherine Phillips under the counsel of Dr. Hans Clarke have been directed toward further purification of the commercial product to minimize still further or to remove, if possible, all toxicity from the active principle. Attempts to purify commercial bacitracin by treatment with sodium chloride indicated that over 96 per cent of the active material could be precipitated. The product showed no improvement in toxicity.

Drs. Goorley and Brown's work²⁰ on the precipitation of bacitracin with iodine as a means of checking antibiotic activity chemically was repeated. A relatively large batch of bacitracin (Lot No. 481101) was subjected to iodine precipitation. The precipitate was decomposed with an excess of finely divided silver in a medium containing water, acetic acid and methanol. The clear, almost colorless filtrate from this reaction was evaporated to dryness under reduced pressure. The residue (about 75 per cent of original weight) showed unaltered activity but no improvement in toxicity.

Fractional precipitation with picric acid was also carried out on a Commercial

Solvents preparation. The antibiotic-picric acid was regenerated from the resulting precipitates by treatment with hydrochloric acid and extraction of picric acid with ether. However, since potency was not increased nor toxicity removed, further attempts to purify bacitracin were continued by means of liquid-liquid extractions following the activity with nitrogen and sulfur determinations. The work on the separation of the amino acid components is being continued in the Columbia laboratories as well as further attempts to separate antibiotic and toxic factors from bacitracin produced in industrial laboratories.

STUDIES IN EXPERIMENTAL GAS GANGRENE

Sandusky has continued his excellent experimental studies on gas gangrene in guinea pigs and found that bacitracin was capable of preventing the development of the lesion in all but one of a series of 171 animals injected with *Cl. welchii*, while 109 of 130 controls died of the infection. He had some late deaths in his animals, thought to be due to some toxic effect of the drug, and he confirmed our conclusion that different lots differed significantly in this toxicity.²¹

ANALYSIS OF THE WHOLE CLINICAL SERIES

The clinical results were grouped in four categories. The result was considered to be "excellent" if the response was sudden or dramatic and the infection brought under control within seventy-two hours; "good" if there was a definite response but somewhat slower in its evolution; "questionable" if the observer believed that the case might have done just as well without the drug as with it; and "no effect" when it was obvious that the infection had run its course regardless of the treatment. The over-all results are shown in Table II.

Of the 270 patients in the series so far treated, about three-fifths had failed to respond to other treatment or a combination of treatments and yet 55.6 per cent of these gave a favorable response to bacitracin. If it had not been available, many of these patients would have gone on with

their infections with prolonged illness, permanent or temporary disability or death. These have therefore been called "salvaged cases." One hundred twenty-six of these cases had failed to respond to penicillin alone or to penicillin in combination with

TABLE II
OVER-ALL RESULTS OF SYSTEMIC BACITRACIN TREATMENT
IN 270 CASES ACCORDING TO DIAGNOSIS

Diagnosis	Total Cases	Results of Treatment			
		Excellent	Good	Questionable	No Effect
Cellulitis	31	16	10	2	3
Pneumonia	27	16	2	0	9
Infected accidental wound	20	6	12	1	1
Deep abscess	19	5	10	2	2
Infected operation wound	14	2	5	2	5
Chronic osteomyelitis	12	0	4	4	4
Carbuncle(s)	8	1	6	0	1
Endocarditis	8	0	0	1	7
Prophylactic	7	1	6	0	0
Ulcer(s) of leg(s)	7	0	4	2	1
Undermining burrowing ulcer	6	2	2	0	2
Staphylococcal meningitis	5	5	0	0	0
Synergistic gangrene	5	4	1	0	0
Acute osteomyelitis	4	0	3	0	1
Superficial abscess	4	0	2	1	1
Multiple furuncles	4	0	1	1	2
Ulcerative colitis	4	0	0	2	2
Human bite infection	3	2	0	0	1
Furuncle	3	0	3	0	0
Actinomycosis	3	0	1	2	0
Miscellaneous (2 each)	32	5	13	3	11
Miscellaneous (1 each)	44	5	22	9	8
Totals	270	70	107	32	61
	Favorable results in 65.6% of cases				

other drugs. The three largest groups were "penicillin only" in which there were thirty-seven cases, "penicillin with some sulfonamide" thirty-one, and "penicillin, streptomycin and some sulfonamide" twenty-eight. Of the ninety-six cases in these three main categories of penicillin treatment there were twenty-three which gave a brilliant response to bacitracin and in thirty-two it was called "good"—a total favorable result of 57 per cent.

Of the 119 cases that had had no previous antibiotic treatment, the favorable responses to bacitracin were 78.1 per cent. This difference can be largely explained on the basis of earlier treatment in the latter group.

About half of the cases were treated with systemic bacitracin alone and the others

with both systemic and local bacitracin. The favorable results in the latter series (75.6 per cent) were considerably better than in the former (56.4 per cent), but these series are not strictly comparable because in the former group the infections were more serious, the inflammation was more diffuse and was often not sufficiently localized to permit local treatment. Moreover, many of these cases did not have the benefit of surgical drainage.

Bacteriologic studies in these cases revealed that the majority were infected with a mixture of organisms. This was especially true in the chronic cases which had lasted for a month or more before treatment with bacitracin began, and yet the response to bacitracin was almost if not just as good in these mixed infections as in the pure infections. This was probably due to the fact that bacitracin has a very wide antibacterial spectrum and is not inhibited as is penicillin by the penicillinase producers which are so frequently present in mixed infections.

Most of the organisms found associated with these infections were tested for their susceptibility to both penicillin and bacitracin. One hundred twenty-two species were susceptible to both, 104 were susceptible to bacitracin but not to penicillin while only eleven were resistant to bacitracin and susceptible to penicillin. Where there was a difference, therefore, the ratio was about 10 to 1 in favor of bacitracin. This ratio is twice as great as appeared in a similar study of patients treated locally with bacitracin two years ago.⁴ Furthermore, the ratio is favorable to bacitracin in every bacterial group. This would suggest that as time goes on more and more infections will be found to be due to organisms which are resistant to penicillin and are susceptible to bacitracin.

If this comparison of bacterial susceptibility to bacitracin and penicillin is analyzed further so as to reveal the difference between the group which had been previously treated with systemic penicillin and the group which had not, the ratio of bacitracin to penicillin is found to be 35 to 1 in the

former, while in the latter group the ratio is less than 4 to 1. This is clearly shown in Tables III and IV.

These figures would seem to indicate clearly that many organisms had built up a resistance to penicillin in response to

TABLE III
SUSCEPTIBILITY AND RESISTANCE TO BACITRACIN AND
PENICILLIN OF CERTAIN OF THE BACTERIA CULTURED
FROM THE LESIONS OF CASES WITH PREVIOUS
PENICILLIN TREATMENT

Bacteriology	Baci- tracin S. Peni- cillin S.	Baci- tracin S. Peni- cillin R.	Baci- tracin R. Peni- cillin S.	Baci- tracin R. Peni- cillin R.
Hemolytic strept.	13	9	0	3
Non-hemolytic strept.	6	9	0	1
Coag. pos. staph.	12	27	0	2
Coag. neg. staph.	6	3	1	1
Coag. not tested staph. ...	1	13	1	0
Other aerobic cocci.	3	2	0	1
Anaerobic cocci.	8	3	0	3
Gram-neg. bacilli.	0	2	0	52
Gram-pos. bacilli.	2	3	0	5
Clostridia.	3	0	0	0
Totals.	54	71	2	68

S.—Susceptible

R.—Resistant

Note—Cases with previous treatment unknown are not included.

systemic treatment with it. With wider use of bacitracin, resistance to it probably will in turn be gradually built up.

In many instances a synergism could be demonstrated between penicillin and bacitracin in the inhibition of bacterial growth. Often one-tenth of the inhibiting dose of one added to one-tenth or one-fifth of the inhibiting dose of the other would completely prevent the growth of the test organisms. In a number of cases there seemed to be clinical confirmation of this synergism *in vivo*. This interesting feature of antibiotic therapy warrants further study and is of great practical value both from the point of view of effecting a higher percentage of cures in the treatment of infections and of making economical use of these materials.

DECEMBER, 1949

Whether or not bacitracin can be further purified and the toxicity be as completely removed as in the case of penicillin and streptomycin remains to be seen. Nevertheless, the presently available product which meets the specification of LD-50 of 500 units

TABLE IV
SUSCEPTIBILITY AND RESISTANCE TO BACITRACIN AND
PENICILLIN OF CERTAIN OF THE BACTERIA CULTURED
FROM THE LESIONS OF CASES WITH NO PREVIOUS
PENICILLIN TREATMENT

Bacteriology	Baci- tracin S. Peni- cillin S.	Baci- tracin S. Peni- cillin R.	Baci- tracin R. Peni- cillin S.	Baci- tracin R. Peni- cillin R.
Hemolytic strept.	9	4	1	0
Non-hemolytic strept.	4	3	0	1
Coag. pos. staph.	13	7	2	1
Coag. neg. staph.	4	4	0	0
Coag. unknown staph. ...	12	5	5	0
Other aerobic cocci.	1	1	0	1
Anaerobic cocci.	6	0	0	1
Gram-neg. bacilli.	0	2	0	11
Gram-pos. bacilli.	3	2	0	4
Clostridia.	3	2	0	1
Totals.	55	30	8	20

S.—Susceptible

R.—Resistant

Note—Cases with previous treatment unknown are not included.

for a 20-gram mouse is sufficiently safe to warrant its widespread use in cases in which the infecting organisms are susceptible to bacitracin and resistant to other antibiotics or which have failed to respond to other methods of treatment.

SUMMARY

1. Bacitracin is an antibiotic produced by a strain of *B. subtilis* recovered from the débrided tissue removed from a compound fracture. It has a wide antibacterial spectrum and is not inhibited by the penicillinase producers.

2. Bacitracin has been produced commercially and is available as a lyophilized powder which has been accepted by the Food and Drug Administration for local use in the treatment of infections. These

infections have responded favorably in the great majority of cases when the drug was applied locally in the form of a solution, or in an ointment base, or when the solution was injected locally into the inflamed tissues or instilled after the aspiration of a purulent exudate from an abscess cavity.

3. Many patients with surgical, dermatologic and ophthalmologic infections have been reported successfully treated in this manner without any evidence of toxicity and with minimal allergenicity.

4. Bacitracin has been found to be lethal for *Endameba histolytica* and has been effective by oral administration in the treatment of amebiasis. It is not toxic when given by mouth and is not readily absorbed.

5. Bacitracin is retained in the alimentary tract and acts upon many of the intestinal bacterial species.

6. Bacitracin has been administered by intramuscular injection in the systemic treatment of various types of infections in 270 cases, with a favorable response in about two-thirds of the patients. More than half of this series had failed to respond previously to other methods of antibacterial therapy, and more than half of these responded favorably to bacitracin.

7. Some of the patients treat intramuscularly with bacitracin showed disturbing symptoms and signs of kidney irritation but these can be reduced to a minimum if the commercial product can consistently meet a specification of LD-50 of 500 units for a 20-gram mouse.

8. There is evidence that there is a synergistic action between penicillin and bacitracin in the control of infections.

9. Chemical studies are being pursued in an effort to purify this drug further, to identify the active principle and to separate it if possible from the toxic factor so that it may be administered in large quantities as safely as is penicillin.

REFERENCES

1. JOHNSON, B. A., ANKER, H. and MELENEY, F. L. Bacitracin: a new antibiotic produced by a member of the *B. subtilis* group. *Science*, 102: 376-377, 1945.
2. ANKER, H. S., JOHNSON, B. A., GOLDBERG, J. and MELENEY, F. L. Bacitracin: methods of production, concentration and partial purification, with a summary of the chemical properties of crude bacitracin. *J. Bact.*, 55: 249-255, 1948.
3. SCUDI, J. V., CORET, I. A. and ANTAPOL, W. Some pharmacological characteristics of bacitracin III. Chronic toxicity studies of commercial bacitracin in the dog and monkey. *Proc. Soc. Exper. Biol. & Med.*, 66: 558-561, 1947.
4. MELENEY, F. L. and JOHNSON, B. A. Bacitracin therapy. The first hundred cases of surgical infections treated locally with the antibiotic. *J. A. M. A.*, 133: 675-680, 1947.
5. SCUDI, J. V. and ANTAPOL, W. Some pharmacological characteristics of bacitracin. *Proc. Soc. Exper. Biol. & Med.*, 64: 503-506, 1947.
6. SCUDI, J. V., CLIFT, M. E. and KRUEGER, R. A. Some pharmacological characteristics of bacitracin II. Absorption and excretion of bacitracin in the dog. *Proc. Soc. Exper. Biol. & Med.*, 65: 9-13, 1947.
7. BOND, G. C., VANDERBROOK, M. J., WILEY, J. L. and NOOK, M. A. Oral administration of bacitracin. *Proc. Soc. Exper. Biol. & Med.*, 68: 395-400, 1948.
8. EAGLE, H. and FLEISHMAN, R. Therapeutic activity of bacitracin in rabbit syphilis, and its synergistic action with penicillin. *Proc. Soc. Exper. Biol. & Med.*, 68: 415-417, 1948.
9. EAGLE, H. Data to be published.
10. MILLER, J. L., SLATKIN, M. H. and JOHNSON, B. A. Local use of bacitracin. *J. Invest. Dermat.*, 10: 179-188, 1948.
11. FAUST, E. C. Personal communication.
12. MOST, H. Data to be published.
13. LONGACRE, A. B. Personal communication.
14. TENG, P. and MELENEY, F. L. Bacitracin levels in the cerebrospinal fluid after parenteral injections. Bacitracin therapy of experimental staphylococcal meningitis in the dog. Accepted for publication in *Surgery*.
15. REISNER, E. H., JR., BAILEY, F. N. and APPLEBAUM, E. The treatment of pneumonia with bacitracin. *Ann. Int. Med.*, to be published.
16. MELENEY, F. L., ALTEMEIER, W. A., LONGACRE, A. B., PULASKI, E. J. and ZINTEL, H. A. The results of the systemic administration of the antibiotic, bacitracin, in surgical infections. A preliminary report. *Ann. Surg.*, 128: 714-731, 1948.
17. MICHIE, A. Personal communication.
18. MELENEY, F. L., LONGACRE, A. B., ALTEMEIER, W. A., REISNER, E. H., JR., PULASKI, E. J. and ZINTEL, H. A. The efficacy and the safety of the systemic administration of bacitracin in various types of surgical and certain medical infections with an analysis of 270 cases. *Surg., Gynec. & Obst.*, to be published.
19. CRAIG, L. C., GREGORY, J. D. and BARRY, G. T. Purity studies on polypeptide antibiotics: bacitracin. Read before the Second National Symposium on Recent Advances in Antibiotics Research in Washington, D. C., April 12, 1949.
20. BROWN, M. Personal communication.
21. SANDUSKY, W. R., KEEBLE, E. F. and WHARTON, W. P. The use of bacitracin in experimental clostridial infections. Accepted for publication in *Ann. Surg.*

The Polymyxins*

A Review and Assessment

PHILIP G. STANSLY, Ph.D.

Stamford, Connecticut

POLYMYXIN is a generic term for a group of related antibiotics derived from *Bacillus polymyxa*, a spore-forming rod occurring in soil. The various polymyxins are relatively simple, basic polypeptides which form water-soluble salts with mineral acids. Biologically they are characterized by their high activity against gram-negative bacteria and their therapeutic activity in systemic infections produced by susceptible micro-organisms.

CHEMISTRY

Four distinct polymyxins have been isolated from the metabolism liquor of different strains of *B. polymyxa* and are designated polymyxins A, B, C and D.¹ Polymyxin A was formerly called "Aerosporin" and polymyxin D "Polymyxin." The peptide nature of the polymyxins, which have molecular weights of at least 1,000, is well-established and their amino acid composition has been determined.²⁻⁴ These are given in Table I. It can be seen that each of the polymyxins consist of only three or four α -amino acids, and that those common to all are α, γ -diaminobutyric acid and threonine. The isolation of α, γ -diaminobutyric acid from the polymyxins represents the first demonstration of this amino acid as a constituent of a natural product.

The configuration of the amino acids in polymyxins A and D has been established as L (so-called "natural" configuration) for α, γ -diaminobutyric acid and threonine, and D (so-called "unnatural" configuration) for leucine and serine.

In addition to the amino acids shown in

Table I the polymyxins also contain an optically active branched-chain fatty acid of empirical formula $C_{18}H_{35}O_2$ which is identical in polymyxins A, B and D. According to Catch et al.⁴ the substance is 6-methyloctanoic acid and is thought to

TABLE I
AMINO ACID COMPOSITION OF THE POLYMYXINS

Poly- myxin	α, γ -Di- amino- butyric Acid	Threo- nine	Leucine	Phenyl- alanine	Serine
A	+	+	+		
B	+	+	+	+	
C	+	+		+	
D	+	+	+		+

+ denotes presence of amino acid.

exist as an N-acyl group in the polymyxin molecule.

There is ample evidence from partition chromatography and solvent distribution studies² for the elaboration by polymyxin D-producing strains of *B. polymyxa* of smaller quantities of biologically active components which appear to have the same qualitative and quantitative composition as polymyxin D but differ from it physically and possibly biologically. Jones³ also describes a polymyxin (polymyxin E) the qualitative composition of which is identical with that of polymyxin A but the speed of which in partition chromatography approximates B.

The polymyxins are stable under physiologic conditions of pH and temperature either in aqueous solution or as a powder. On the other hand, polymyxin D and pre-

* From the Chemotherapy Division, Stamford Research Laboratories, American Cyanamid Company, Stamford, Conn.

sumably the other polymyxins are unstable under alkaline but not acid conditions, the rate of destruction depending upon the pH and temperature.⁵ Polymyxins A and D are unaffected by proteolytic enzymes.^{6,7}

The remarks which follow are concerned with polymyxins A, B and D. No experimental investigations have been reported for polymyxins C or E.*

ANTIBACTERIAL ACTIVITY IN VITRO

The outstanding antibiotic property of the polymyxins is their specificity for gram-negative bacteria and, as a corollary, their almost uniform lack of activity against gram-positive bacteria. To those concerned with problems of this nature the polymyxins may provide a useful tool in elucidating fundamental distinctions between these two groups of micro-organisms. Available information indicates^{6,8} that polymyxins A, B and D of comparable purity do not differ materially in their effect on bacteria *in vitro* either qualitatively or quantitatively.

As might be expected, refractory organisms in the gram-negative group occur. Members of the genus *Proteus* are generally resistant although exceptions to this exist.⁵ All other genera studied are sensitive. These include *Aerobacter*, *Brucella*, *Eberthella*, *Escherichia*, *Hemophilus*, *Klebsiella*, *Pasteurella*, *Pseudomonas*, *Salmonella*, *Shigella* and *Vibrio*. Occasional resistant species or strains are encountered, however, and some variation in sensitivity from genus to genus, species to species and strain to strain have been observed. Some *Neisseria* have been found sensitive to A and D, others resistant. A peculiar finding¹⁰ is the resistance *in vitro* of a strain of *N. intracellularis* against which, however, polymyxin D was effective in mice.

The size of inoculum has an appreciable effect on the titration end points of the polymyxins. Thus increasing the inoculum by ten-fold steps from about 2 cells to 20,000,000 cells of *E. coli* per ml. raised the

end point also stepwise from 0.02 to 6 $\mu\text{g.}$ / ml. of polymyxin D.⁸

The activity of the polymyxins does not appear to be appreciably affected by the composition or pH of the test medium or by the inclusion of blood or serum.^{5,11} Bliss et al.¹¹ noted moderate antagonism of polymyxin D by soap, lecithin and lipositol.

A notable feature of the polymyxins is the difficulty experienced by most investigators in developing resistant strains from sensitive species.^{5,10,12,15} Presumably, therefore, resistant mutants are rare. Nevertheless, resistant strains have been obtained experimentally in some instances.^{5,13}

There is general agreement that the polymyxins are rapidly bactericidal and that this is the primary antibiotic action. As an indication of the speed of sterilization, Bliss et al.¹¹ found that when 100,000 cells per ml. of *E. coli* were exposed to 0.2 $\mu\text{g.}$ / ml. of polymyxin D in broth, only 20 viable cells per ml. remained after one hour and one after three hours.

A phenomenon which may have bearing on the mechanism of action of the polymyxins is the apparent lytic effect on sensitive species by polymyxins A and D noted by White et al.⁸ This was evidenced by a rapid decrease in the turbidity of a cell suspension exposed to moderate concentrations of the antibiotics. Heat-killed cells were not affected. Under similar conditions streptomycin failed to cause any change. Not all polymyxin-sensitive strains were "lysed," however. Hence there is no clear cut relation between bactericidal and "lytic" activity.

EXPERIMENTAL CHEMOTHERAPY

The therapeutic effectiveness of polymyxins A, D and, to a lesser extent, B has been determined for a variety of experimental gram-negative infections, particularly in mice. In general, the *in vivo* results parallel the *in vitro* results; that is, infections produced by organisms sensitive to the antibiotic *in vitro* were favorably influenced; infections produced by organisms resistant to the polymyxins *in vitro*, including gram-

* Polymyxin E has been used clinically by Pulaski and Rosenberg.¹⁰ However, E is not treated separately or otherwise distinguished from B in this study.

positive organisms, were unaffected. The one known anomaly in this regard is that previously mentioned concerning a strain of meningococcus.¹⁰

Experimental chemotherapy has been studied with fewer organisms but in greater detail with polymyxin D⁵ than A or B. A typical experiment relating dose to chemotherapeutic effect of polymyxin D in an otherwise rapidly fatal experimental infection with *K. pneumoniae* in mice is illustrated in Table II and requires no further comment. In agreement with the *in vitro* results, increasing the inoculum increased the dose required to obtain the same therapeutic response. If treatment was delayed after infection, the dose required for a given therapeutic effect was also increased,¹⁴ probably reflecting, in part, the increased number of organisms in the mouse.

A single dose of polymyxin D was found to be more effective than the same amount given in divided doses. Thus in the case of *K. pneumoniae* in mice¹⁴ a single dose of 1 mg./Kg. at the time of infection protected 85 per cent of the mice; 0.5 mg./Kg. at once followed by 0.5 mg./Kg. at three, six or twenty-five hours protected 70, 65 and 55 per cent, respectively; 0.25 mg./Kg. at once and repeated at three, six and twenty-four hours, resulted in only 5 per cent survivors.

Parenterally administered polymyxin D was more effective than orally administered drug. It was found⁵ that in the case of *K. pneumoniae* in mice oral administration required about sixty-four times as much drug to obtain the same therapeutic response as when administration was by the subcutaneous or intravenous route.

Other experimental infections favorably influenced by polymyxin D were *Pasteurella multocida*,^{5,8} *H. influenzae* b,¹⁴ *H. pertussis*⁸ and *E. typhosa* in mice,⁹ and *Shigella gallinarum* in fowl.⁵

Experimental mouse infections studied by Brownlee et al.^{6,15} and found to be favorably influenced by polymyxin A were *E. typhosa*, *E. coli*, *H. influenzae*, *K. pneumoniae*, *H. bronchisepticus*, *H. per-*

tussis and *Ps. pyocyanea*. In the few studies with polymyxin B⁶ the results obtained were comparable to polymyxin A.

In direct comparisons of polymyxins A and D of comparable purity White et al.⁸ found D to be 30, 50 and 90 per cent as

TABLE II*

THERAPEUTIC ACTIVITY OF POLYMYXIN HYDROCHLORIDE AGAINST *KLEBSIELLA PNEUMONIAE*, STRAIN BE, IN MICE

Mice: Vanderwerken; 16–24 Gm.

Infection: Intraperitoneal; 0.5 cc. of 10⁻⁵ dilution of a 4-hour broth culture; 5,000 ± 2,000 organisms.

Treatment: Subcutaneous; single dose given immediately after infection; aqueous solutions of drug at pH 7.0 ± 0.2.

Dosage† mg./Kg.	Survival—21 Days after Infection		
	Alive/Total	Per Cent	Time‡
4.0	70/70	100	
2.0	70/70	100	
1.0	70/70	100	
0.8	76/80	95	4.5
0.6	69/80	86	5.6
0.4	40/80	50	3.8
0.2	0/80	0	1.7
Untreated	0/80	0	1.3

* From Polymyxin: a new chemotherapeutic agent. P. G. STANSLY, R. G. SHEPHERD and H. J. WHITE. *Bull. Johns Hopkins Hosp.*, 81: 43–54, 1947. With permission of the Editors.

† Dosage expressed as pure polymyxin hydrochloride, 2,000 units per mg.

‡ Average survival time (days) for mice that died.

effective as A in experimental infections produced in mice by *H. pertussis*, *K. pneumoniae* and *P. multocida*, respectively. A parallel study by Brownlee et al.⁹ with other organisms gave similar results except for *H. pertussis*, in which case Brownlee considered polymyxin D to be one-seventh as effective as polymyxin A. Both groups of investigators were in agreement that polymyxin D was approximately one-half as acutely toxic for mice as polymyxin A.^{6,8}

As was suggested by the *in vitro* results, both polymyxin A¹⁵ and D¹⁰ were found to be about ten times more effective weight for weight than streptomycin in experimental infections in mice produced by susceptible bacteria.

EXPERIMENTAL AND CLINICAL
PHARMACOLOGY

It should be borne in mind that pharmacologic and clinical data have been obtained with polymyxin preparations of about 70 per cent purity. The impurities may be of minor importance in absorption and distribution of the antibiotics but may play a significant role in producing toxic effects. Unfortunately, the effect of impurities has not been evaluated and we are obliged to consider toxic reactions, whenever they occur, as being due to the antibiotic unless it is proved otherwise.

Lethal Toxicity of Polymyxins A, B and D in Experimental Animals. In mice the acute lethal dose of the polymyxins is dependent upon the route of administration. Thus Brownlee et al.⁶ found the relative lethal dose (LD₅₀) for the intravenous, intraperitoneal and subcutaneous routes to be in the approximate order of 1, 2 and 13. This relationship held for each of the antibiotics. With a lethal dose the time at which death occurs is also dependent upon the route of administration, being two to thirty minutes after intravenous, two to four hours after intraperitoneal and up to thirty-six hours after subcutaneous administration for all three antibiotics. For all three routes and for material of equivalent potency, polymyxin D was found to be about one-half as acutely toxic as polymyxins A or B.^{6,8} As an indication of the absolute amount of a polymyxin required to produce death the results of Bryer et al.¹⁴ are of interest. They determined the LD₅₀ for two lots of polymyxin D administered as a single dose subcutaneously in mice. One lot had an LD₅₀ of 250 to 300 mg./Kg. and the other 400 to 500 mg./Kg. The symptoms preceding death were ataxia, convulsions, paralysis and respiratory arrest.

Dogs survived single intravenous injections of 10 to 15 mg./Kg. of polymyxin D. Rapid intravenous injection of 25 mg./Kg. or intravenous drip with a total of 35 mg./Kg. was fatal.¹⁴ The symptoms observed included paralysis and apnea, death occurring at twenty minutes and two and one-

half hours, respectively. Doses of 5 or 10 mg./Kg. intramuscularly twice daily for seven days were well tolerated. Intrathecal injections of 1 or 5 mg. produced no untoward reaction while 10 mg. produced a transient paresis of the hind legs.

Experimental and Clinical Absorption, Distribution and Excretion. Therapeutic blood levels are readily attained by parenteral administration of polymyxins A, B and D. Absorption from the gastrointestinal tract also takes place, at least with polymyxins B and D. With adequate dosage therapeutic effects in systemic infections are obtainable by this route both experimentally⁵ and clinically.¹⁶

Polymyxin A: The information available on polymyxin A is meager. Subcutaneously administered in rabbits it appears promptly in the plasma but not in the red cells of the blood nor in the spinal fluid.¹⁵ Swift¹⁷ obtained serum levels of from 0.2 to 1.6 μ g./ml. one hour following an intramuscular injection of from 2.1 to 4.0 mg. in children of one month to two and one-half years of age.

Polymyxin B: Polymyxin B was administered by Kaplan et al.¹⁸ to a group of children intramuscularly (0.8 mg./Kg. every four hours for five days) or by aerosol inhalation (0.5 mg./Kg. four times daily for five days). Serum levels determined in twenty-six cases three and one-half to four hours following intramuscular administration gave 2.8 to 7.0 (av. 4.6) μ g./ml. Thirteen cases in the aerosol group gave 2.0 to 2.6 (av. 2.3) μ g./ml. after one hour. Cumulative effects were not observed since levels were approximately the same on the third, fourth or fifth days of treatment. Ross et al.¹⁶ also found in children that a dosage of 3 mg./Kg. orally every four hours, combined with 0.5 mg./Kg. intramuscularly every four hours, gave spot blood levels of 1.4 to 4.2 μ g./ml. No detectable blood level was found upon oral administration alone. It was inferred, however, that absorption took place since one-third of the patients showed elevated blood non-protein nitrogen attributed to the nephrotoxic effect of the drug.

Pulaski and Rosenberg¹⁹ noted that in man the peak serum concentration occurred two hours following intramuscular administration of 2 to 4 mg./Kg. At six hours one-half of the peak concentration was still present, and at twelve hours there was still a measurable level. Cumulative serum concentrations were observed if the doses were more frequent than at twelve-hour intervals. They noted that although excretion of polymyxin B was primarily renal it was slower than that of penicillin or streptomycin. During the first twelve hours after injection less than 0.1 per cent of the dose was recovered in the urine, but following this a progressive increase in urinary excretion occurred. When the daily dose was 3 mg./Kg., the concentration in the urine after twenty-four hours ranged from 40. to 400 $\mu\text{g.}/\text{ml.}$

Polymyxin D: In dogs¹⁴ single intramuscular doses of 5 and 10 mg./Kg. gave serum levels of 2.5 and 5.0 $\mu\text{g.}/\text{ml.}$ after one and one-half hours, decreasing to 1.25 and 2.5 $\mu\text{g.}/\text{ml.}$ after three and one-half hours. Levels four times these were obtained with similar doses twice daily for seven days. Practically all the antibiotic disappeared from the serum twenty-three hours after the last injection. No polymyxin was detected in the spinal fluid even with serum levels as high as 320 $\mu\text{g.}/\text{ml.}$ obtained by intravenous drip. Intrathecal administration of 1, 5 and 10 mg. resulted in spinal fluid levels of 10 to 500 $\mu\text{g.}/\text{ml.}$ which fell to 0.3 to 20 $\mu\text{g.}/\text{ml.}$ in two to five hours. Blood levels of 1.25 to 0.6 $\mu\text{g.}/\text{ml.}$ were obtained with the 5 and 10 mg. doses.

In man²⁰ intramuscular administration of 3 mg./Kg./day in divided three-hourly doses gave blood levels of 0.6 to 1.3 $\mu\text{g.}/\text{ml.}$ within twelve hours. On continued treatment the level rose to 2.5 and 5 $\mu\text{g.}/\text{ml.}$ Accumulation of drug was not apparent.

When administered in daily doses of 4 to 7 mg./Kg. a lag in urinary excretion of approximately twelve hours was noted, paralleling the observation made by Pulaski and Rosenberg¹⁹ with polymyxin B. Drug then appeared in the urine, increasing

rapidly so that by seventy-two to ninety-six hours approximately 60 per cent of the administered drug was excreted. The concentration in the urine varied between 10 and 100 $\mu\text{g.}/\text{ml.}$

Toxic Reactions. Polymyxins A and B: According to Brownlee and Bushby¹⁵ all batches of polymyxin A contained an antidiuretic factor for rats on "high dose" levels. Antidiuresis, however, was not observed in man on "therapeutic" dosage. All batches but one caused damage of the renal tubules which was accompanied by albuminuria. The effect was at first said to vary inversely with purity but subsequent data did not support this conclusion.⁶ The antidiuretic and tubule-damaging factors were thought to be distinct.

Brownlee et al.⁶ attempted to counteract the tubular effects of polymyxin A in rats by treatment with a variety of amino acids and related compounds. D,L-methionine was considered to be significantly active. In dogs the data indicated that complete protection against the effect of 1 mg. of polymyxin A four times daily was afforded by a single injection of 5 mg./Kg. of methionine. This salutary effect of methionine in counteracting albuminuria caused by polymyxin A did not carry over to man.^{6,22}

Comparisons of the renal toxicity of polymyxin A and B were made in the rat, rabbit, dog and, to a minor extent, in man. The protocols, unfortunately, suffer from a lack of clarity. For instance, in the rat experiment the doses administered are not given. In the data on man the two subjects on polymyxin B received one-half and one-fifth, respectively, of the dose the subjects on polymyxin A received. Furthermore, in several instances an element of uncertainty exists as to whether or not the dose was adjusted in accordance with the varying potencies of the batches of drug used. The rabbit and dog experiments were less confusing and the data in these suggest that less proteinuria was associated with administration of polymyxin B than A.

In man the most serious symptoms associ-

ated with administration of the polymyxins are those attributable to renal damage. Of lesser importance are certain subjective nervous symptoms associated with administration of polymyxin B and, possibly, of E. Finally, minor disturbances, such as elevated temperatures, malaise, etc., have also occurred with the various polymyxins.

Ross et al.¹⁶ treated patients orally with polymyxin B, or both orally (2 to 3 mg./Kg. every four hours) and intramuscularly (0.5 mg./Kg. every four hours). Only six cases comprised the latter group. The majority of toxic reactions occurred after intramuscular administration. Malaise and anorexia were noted in three of the six patients. Blood non-protein nitrogen did not increase significantly. Albuminuria, ranging from 15 to 200 mg. per cent, was observed in two of the six cases while casts and white cells were seen in five. In all instances urinary and blood abnormalities disappeared within two to four days after termination of therapy.

Pulaski and Rosenberg¹⁹ studied twenty cases of severe urinary tract infections treated with polymyxins B or E. Treatment was intramuscular for two to six days. None of the patients developed drug sensitivity. When the dosage did not exceed 2.5 mg./Kg./day, there was no increase in blood urea, blood non-protein nitrogen or any consistent evidence of nephrotoxicity. When the dosage exceeded 4 mg./Kg., the amount of albumin and the number of red, white and renal cells in the urine increased. Granular casts were seen only inconstantly. Oliguria and fixation of the specific gravity of the urine at a low level were not consistently observed. In any case urinary abnormalities produced as a result of therapy disappeared within a week after the drug was withdrawn.

In practically every instance, however, nervous phenomena were associated with administration of these two polymyxins. These symptoms consisted of paresthesias and hypesthesias about the face and scalp, mild dizziness and weakness. The symptoms persisted throughout treatment and disappeared within twenty-four hours after

completion of therapy. The symptoms were not severe enough to warrant cessation of therapy. Adrenalin, intravenous calcium or antihistaminics did not produce relief. Objective neurologic abnormalities could not be demonstrated.

Jawetz and Coleman¹³ also call attention to the neurologic disturbances accompanying therapy with polymyxin B. They lasted while the drug was administered and subsided thirty-six to forty-eight hours after it was discontinued. No residual effects were observed. In their series of ten adults treated intramuscularly with doses of 20 mg. (about 0.5 to 1.0 mg./Kg.) every four to eight hours for three to four days no evidence of renal damage was detected.

In Kaplan's et al.¹⁸ series of eighty-four children treated intramuscularly (0.8 mg./Kg. every four hours for five days) or by inhalation (about 0.5 mg./Kg. four times daily) with polymyxin B, albuminuria was present in thirty-three of sixty-six intramuscularly treated patients, varying from a trace to 3 plus and frequently associated with white cells. In all cases the urinary findings disappeared after treatment was discontinued. The most distressing symptoms noted were marked lethargy, irritability and anorexia in all intramuscularly treated patients. These symptoms persisted until therapy was ended. Oliguria was present in several patients but was believed to be secondary to anorexia. As might be expected, toxicity was less pronounced with aerosol-treated patients because of the lower blood levels obtained.

The only available information concerning polymyxin A is that of Swift¹⁷ who treated ten children intramuscularly with 2.1 to 4.0 mg. (about 0.5 mg./Kg.) of polymyxin A usually at four-hour intervals for varying periods up to seven days. Transient albuminuria developed in nine of the ten patients varying from a trace to 400 mg. per cent. In most instances the albuminuria disappeared within a week. Gross hematuria was not observed but red blood cells and granular and hyaline casts were noted in four of the cases.

Polymyxin D: Experimentally Bryer et al.¹⁴ found that a large single daily subcutaneous dose (20 mg./Kg.) of polymyxin D in dogs led within twenty-four hours of the first injection to the appearance of epithelial cells, cellular casts and albumin in the urine. The specific gravity decreased but the urinary output was maintained and usually increased. The administration of D,L-methionine did not prevent the urinary changes. The albuminuria tended to decrease despite continuation of treatment.

Schoenbach et al.²⁰ treated twenty-two patients suffering from a variety of infections with polymyxin D intramuscularly (in one case subcutaneously) with 3 to 7 mg./Kg./day in divided doses. Albuminuria, cellular casts, granular casts and large epithelial cells appeared in some of the patients, particularly in those receiving the larger doses. The more severe effects occurred in those patients with pre-existing renal impairment. In some patients the albuminuria disappeared even though treatment continued. Azotemia was noted in four patients and oliguria in one. Epigastric distress with anorexia was noted on five occasions with four patients but disappeared during treatment. Blood counts and liver function tests were normal.

General: Practically all who have studied the polymyxins clinically report an occasional rise in temperature associated with parenteral administration. On the other hand, Kaplan et al.¹⁸ found that sixty-two of sixty-four patients on polymyxin B reacted in this way and developed an average temperature of 101° to 102°F. for as long as therapy was continued.

Pain at the site of intramuscular injection was another frequent complaint, and was relieved in most instances by administration of the drug in 1 per cent procaine or similar anesthetic. According to Kaplan et al. less pain was associated with polymyxin B sulfate than hydrochloride.

Both Brownlee et al.⁶ and Bryer et al.¹⁴ are in agreement that the renal damage produced by the polymyxins is confined to the tubular epithelium. The effect on the

tubular epithelium is reversible, as evidenced by the fact that (1) clinically the proteinuria disappears upon cessation of drug and sometimes decreases even upon continuation of the drug and (2) experimentally there is histologic evidence of tubule regeneration in animals sacrificed while under continuous administration.¹⁴

THERAPY IN MAN

Polymyxin A in Pertussis. Swift's series of ten unselected cases of pertussis is the only report available of the therapeutic use of polymyxin A in man.¹⁷ Diagnosis of pertussis was symptomatic except for one case in which the causal organism was isolated. The patients ranged from one month to two and one-half years old. Administration was 0.4 mg. every 4 hours intramuscularly for 5 days in mild infections, and 0.8 mg. every 3 or 4 hours in severe infections. Blood levels at 4 hours were 0.2 to 0.4 µg./ml.

Two cases (fourteen months and two and one-half years) were early and mild and their recovery was uneventful. Three (two months, six and one-half months and two years) were moderately severe and were considered to be favorably influenced by therapy; paroxysms and vomiting rapidly subsided and whooping ceased between the sixth and thirteenth days. The other five patients (one, one and three-fourths, three, five and seventeen months) were severely ill. In two of these death seemed imminent but one (one month) responded promptly and recovered. The other (seven weeks) was complicated by gastroenteritis. Cyanosis, apnea and whooping rapidly disappeared but the child died of gastroenteritis. The third (three months) responded to a second course of polymyxin A but not to the first. The dose of the first course was believed to be too small. The fourth severe case (five months) recovered rapidly and the fifth (seventeen months), a case of two weeks' duration, was responsive but died of staphylococcal lung abscesses.

Swift concluded that "all these cases showed a definite response in the first forty-

eight hours; the ultimate benefit obtained seemed to depend on the duration of symptoms before the start of treatment rather than on the severity of the disease or the patient's age."

Polymyxin A in Abdominal Surgery. Polymyxin A was included by Pulaski et al.²¹ in a study to evaluate various substances as preoperative antiseptics in gastrointestinal surgery. Twelve patients received 200 or 400 mg. of polymyxin A in divided doses four times daily for as long as sixteen days. All coliform organisms except *Proteus* were suppressed within twenty-four to sixty hours and suppression was maintained for two days after administration was discontinued. There were no toxic reactions.

Polymyxin B in Specific and Non-Specific Enteritis in Children. Forty patients were treated by Ross et al.¹⁶ as follows: eighteen cases of non-specific enteritis, 2 mg./Kg. orally every four hours for four to ten days; sixteen cases of *Shigella* enteritis (sonnei and flexner), 3 mg./Kg. orally every four hours for seven to fifteen days; four cases of *Salmonella* enteritis, orally (3 mg./Kg.) and intramuscularly (0.5 mg./Kg.) every four hours; and two cases of typhoid fever orally (2 mg./Kg.) and intramuscularly (0.5 mg./Kg.) every four hours.

No salutary effect either with respect to the duration or severity of the diarrhea was detected in the patients with non-specific enteritis. The authors note that these results are at variance with the favorable results reported in the majority of some forty odd cases of presumably non-specific gastroenteritis mentioned by Brownlee.²²

Of the sixteen cases of *Shigella* infections fourteen were regarded as having been bacteriologically and clinically cured. The stools became negative for the pathogen in one to four days. Only two of the four cases of *Salmonella* infection received drug long enough to evaluate its effect. One of these was bacteriologically cured while the other suffered a recurrence after cessation of therapy. Therapy in the other two cases was stopped prematurely on account of the appearance of untoward reactions. No

striking clinical effect resulted in the two cases of typhoid although the organisms were very sensitive *in vitro* and the bacteriologic response of the patients was regarded as encouraging.

Polymyxin B in Urinary Tract Infections. Twenty patients with severe urinary tract infection were treated with polymyxin B and E by Pulaski and Rosenberg.¹⁹ All but one of these patients had had previous extended trials with other agents including penicillin, streptomycin and sulfonamides. Polymyxin therapy consisted of intramuscular administration of an average of 2.5 mg./Kg./day generally in four divided doses for periods ranging from two to six days.

Ten of the twenty patients were regarded unequivocally as having been benefited by polymyxin. Improvement was noted by the second day of treatment and was manifested by reduction or elimination of bacteria in the urine, regression of symptoms, decrease in fever and improvement in the urine as determined by complete urinary analysis. The outcome was considered to be particularly gratifying in acute *Pseudomonas* pyelonephritis cases. In all improved patients improvement was sustained for a minimum follow-up of three weeks.

In seven instances the results of polymyxin therapy were considered doubtful. Each of these patients had severe, long-standing pyelonephritis. All the patients, however, had an immediate clinical or bacteriologic response or both but there was either no permanent improvement despite elimination of the organisms or the organisms were not completely eliminated.

Three cases were regarded as failures. One had a *Proteus* organism resistant to polymyxin. The other two had scarred kidneys with multiple cortical foci of infection. One of the latter patients had in addition a mixed infection, one of the organisms being *Proteus*.

Jawetz and Coleman¹³ studied ten cases of urinary tract infection treated with polymyxin B. All had failed to respond to sulfonamides and streptomycin. Administration of polymyxin was intramuscular,

20 mg. every four to eight hours (approximately 0.5 to 1.0 mg./Kg./day) for three or four days. An effort was made to maintain serum levels between 2 and 10 μg /ml. No detailed analysis of the results are given except in one case. The authors summarize their findings as follows: “. . . Polymyxin B . . . eliminated susceptible bacteria from urine and controlled symptoms. The short course of treatment, however, was followed by a bacteriologic relapse within one to three weeks.” The authors regard the therapy as having been, “within its scope, . . . successful.” Prolonged treatment was not attempted because of unfavorable side reactions.

Polymyxin B in Influenzal Meningitis. A single case treated successfully with polymyxin B is given in detail by Kagan.²³ The patient was a thirteen month infant who had received large doses of sulfadiazine and streptomycin and also specific rabbit anti-influenzal serum to no avail. When the child had had meningitis for four weeks and a fatal termination seemed inevitable, therapy with polymyxin B was instituted. Administration was intramuscular and intrathecal on the first day (5 mg./Kg. in divided doses intramuscularly and 1 mg. intrathecally) and intrathecal only on the succeeding five days (3.5 mg./day). The infant was afebrile for the first time on the fifth day and markedly improved on the sixth. He improved rapidly and was discharged as cured fifteen days after inception of polymyxin therapy. The causal organism was sensitive to 0.4 units of polymyxin B per ml. A detailed examination of the infant three months after discharge revealed no abnormalities.

Polymyxin B in Pertussis. Kaplan et al.¹⁸ studied the effect of polymyxin B on eighty-four infants and children. Administration in sixty-six patients was intramuscular, 0.8 mg./Kg. every four hours for five days, and in the remainder by aerosol inhalation, about 3 mg./Kg./day in divided doses four times daily. In both series of patients blood levels were well above those necessary to prevent the growth of *H. pertussis in vitro*.

Of the sixty-six intramuscularly treated patients twenty-three were adjudged as improved, seven as equivocal and thirty-six as failures. A case was considered as improved if clinical improvement took place within seven days of the start of therapy. Of the patients treated by inhalation five were improved, five equivocal and eight failures.

It was concluded that a significant therapeutic effect of polymyxin B in Pertussis was not clearly demonstrated. It seems unfortunate that the duration of illness before the start of therapy was not taken into consideration in this study. It may be recalled that it was Swift's impression that the efficacy of polymyxin A in pertussis was dependent upon the duration of symptoms prior to institution of therapy.

Polymyxin B in the Local Treatment of Wounds. Pulaski and Rosenberg¹⁹ record that topical application of 1 per cent polymyxin in saline or carbowax resulted in sterilization of several *Pseudomonas aeruginosa*-infected granulating wounds.

Schoenbach et al.²⁰ treated twenty-two patients with polymyxin D who suffered with infections produced by a variety of gram-negative organisms. The results are summarized in Table III and those of special interest are amplified below.

Polymyxin D in Pseudomonas Aeruginosa. A case of particular interest was a nine year old boy with generalized exfoliative dermatitis which became infected with *Ps. aeruginosa* and β Str. hemolyticus. He also had a pyelonephritis with *Ps. aeruginosa* as the infecting organism. He was considered to be gravely ill and did not improve despite large doses of penicillin, streptomycin and sulfadiazine. Polymyxin therapy was instituted on the twentieth hospital day at a dosage of 3 mg./Kg./day intramuscularly for twenty days. Blood levels of 0.6 to 2.5 μg /ml. were obtained. Cultures of the urine became negative within twenty-four hours and *Ps. aeruginosa* was completely eliminated from the skin in ten days. Urine examination revealed a 4+ albuminuria and casts on the third day which disappeared while treatment was continued. Blood non-

protein nitrogen was 37 mg. per cent before therapy with polymyxin and was unchanged after twenty days of treatment. Because of the streptococcus, penicillin therapy was continued along with polymyxin. The patient completely recovered.

uneventful convalescence after three days of polymyxin therapy.

Polymyxin D in Brucellosis. Two patients with acute brucellosis were treated for ten to fourteen days. Both experienced relief of symptoms rapidly and became afebrile

TABLE III*
SUMMARY OF CLINICAL TRIALS WITH POLYMYXIN D

Disease	No. Treated	Age of Patients	Treatment		Results	
			Daily Dose mg./Kg.	No. of Days	Cultural	Clinical
<i>Pseudomonas aeruginosa</i> infection . . .	3	8 wk.-9 yr.	3-7	3-20	Excellent	Excellent
Pertussis	5	6 wk.-4 yr.	3-7	4-5	Doubtful	Good
Peritonitis†	1	Adult	3	3	Good
<i>Aerobacter aerogenes</i>	3	Adults	4-7	4	Excellent	Good
<i>K. pneumoniae</i>	2	Adults	3-4	4-15	Excellent	Good
Brucellosis	4	Adults	3-7	10-20	Good	Good, acute; chronic, none
Typhoid	4	11, 16, 27, 62 years	4	2-5	Good	Variable

* From The clinical use of polymyxin. E. B. SCHOENBACH, M. S. BRYER and P. H. LONG. *Ann. New York Acad. Sc.*, 51: 987-997, 1949. With permission of the Editors.

† Etiology unknown

Another case concerned a very severely burned child. The burned areas became infected with *Ps. aeruginosa* and the child was gravely ill. Polymyxin was administered intramuscularly at a dose of 3 mg. /Kg. /day for twelve days. The child became afebrile, the exudate cleared and the cultures became negative. There were no complications and convalescence was uneventful.

Polymyxin D in Pertussis. This study involved five cases. It was the opinion of the investigators that the children under one year appeared to benefit from therapy whereas the older age group was more difficult to appraise.

Polymyxin D in Aerobacter Aerogenes. In two cases blood cultures became negative within twenty-four hours after start of therapy and the patients became afebrile.

Polymyxin D in Peritonitis of Unknown Etiology. One patient with peritonitis secondary to a perforated appendix made an

within three to four days. Both were asymptomatic on follow-up several months later. No untoward reactions were noted as a result of therapy except transitory albuminuria in one.

Polymyxin D in Typhoid. The variability noted in Table III was due to many complicating factors in the three cases studied. One patient was treated in the fourth week of illness when he was in circulatory shock, distended and delirious. He died sixty hours after treatment was instituted. A second patient responded well to minimal doses of polymyxin (which was scarce at the time) but relapsed three weeks after polymyxin was discontinued. A third case was extremely serious and concerned a sixty-two year old man with pneumonia, phlebitis, prostatic obstruction and high fever. No improvement resulted from treatment with penicillin or streptomycin. Blood and stool cultures were found to be positive for *E.*

typhosa. Polymyxin in doses of 4 mg./Kg./day was given intramuscularly for five days. The temperature fell within twenty-four hours and was normal on the fifth day of treatment. Blood and stool cultures became negative and the patient made an uneventful recovery after surgical treatment to relieve the prostatic obstruction.

COMMENTS AND CONCLUSIONS

There can be little doubt that the polymyxins have exhibited effective therapeutic activity in certain infections of man produced by gram-negative bacteria. It is apparent, however, that their application in this field is likely to be limited because of the occurrence of untoward reactions elicited by material used in the clinical trials. They will be limited, for instance, to local therapy, to preoperative preparation in abdominal surgery and to those systemic infections in which the dangers of the disease outweigh those of temporary renal damage. The latter would include infections refractory to the sulfonamides, streptomycin or other therapeutic agents, the causal organisms of which are of the type susceptible to the polymyxins. In these instances the polymyxins may, in the words of Long,²⁴ be life-saving. In other instances, as in infections produced by the *Pseudomonas* group, the polymyxins may, even in their present state of purity, be the drugs of choice.

The toxic reactions elicited by the relatively crude polymyxins which have been used clinically should certainly not be minimized. On the other hand, it is equally important not to overemphasize their occurrence and seriousness. The renal effects, which have received major attention, were elicited inconstantly and in every case appeared to be transitory, sometimes disappearing even upon continued administration. Whether the subjective nervous symptoms associated with administration of polymyxin B are limited to this particular polymyxin is not known. Here, too, however, the effects were transitory. No permanent injury resulting from administration

of the polymyxins in man has yet been reported.

Clinically the fundamental relations of dosage, blood levels, toxicity and therapeutic efficiency have yet to be elucidated, and the scope of the polymyxins in the treatment of infectious diseases determined. It is obvious that much is to be gained if attention is given to supplying qualified investigators with material of increased purity.

In this reviewer's opinion the superiority of one polymyxin over another cannot be considered to have been demonstrated. They do not appear to differ from each other materially in their antibacterial properties. The claim has been made that nephrotoxicity is less frequent and intense with polymyxin B than A or D in experimental animals and is absent in man.⁶ The former observation awaits confirmation and the latter is refuted by clinical experience reported in this review. Ultimately, careful clinical comparisons will be necessary should it develop that the polymyxin type of antibiotic finds a useful place in the therapy of infectious diseases caused by gram-negative bacteria.

REFERENCES

1. STANSLY, P. G. and BROWNLEE, G. Nomenclature of polymyxin antibiotics. *Nature*, 163; 611, 1949.
2. BELL, P. H., BONE, J. F., ENGLISH, J. P., FELLOWS, C. E., HOWARD, K. S., ROGERS, M. M., SHEPHERD, R. G. and WINTERBOTTOM, R. Chemical studies on polymyxin: comparison with "aerosporin." *Ann. New York Acad. Sc.*, 51; 897-908, 1949.
3. JONES, T. S. G. Chemical evidence for the multiplicity of the antibiotics produced by *Bacillus polymyxa*. *Ann. New York Acad. Sc.*, 51: 909-916, 1949.
4. CATCH, J. R., JONES, T. S. G. and WILKINSON, S. The chemistry of polymyxin A. *Ann. New York Acad. Sc.*, 51: 917-923, 1949.
5. STANSLY, P. G., SHEPHERD, R. G. and WHITE, H. J. Polymyxin: a new chemotherapeutic agent. *Bull. Johns Hopkins Hosp.*, 81: 43-54, 1947.
6. BROWNLEE, G., BUSHBY, S. R. M. and SHORT, E. I. The pharmacology of polymyxin A, B and D. *Ann. New York Acad. Sc.*, 51: 952-967, 1949.
7. STANSLY, P. G. and ANANENKO, N. H. Resistance of polymyxin to some proteolytic enzymes. *Arch. Biochem.*, 15: 473-474, 1947.
8. WHITE, H. J., ALVERSON, C. M., BAKER, M. J. and JACKSON, E. R. Comparative biological studies of polymyxin and "aerosporin." *Ann. New York Acad. Sc.*, 51: 879-890, 1949.

9. BROWNLEE, G., BUSHBY, S. R. M. and SHORT, E. I. Comparative biological studies of polymyxin A and polymyxin D. *Ann. New York Acad. Sc.*, 51: 891-896, 1949.
10. SCHOENBACH, E. B., BRYER, M. S., BLISS, E. A. and LONG, P. H. Polymyxin—a note on experimental and clinical investigation. *J. A. M. A.*, 136: 1096-1098, 1948.
11. BLISS, E. A., CHANDLER, C. A. and SCHOENBACH, E. B. *In vitro* studies of polymyxin. *Ann. New York Acad. Sc.*, 51: 944-951, 1949.
12. AINSWORTH, G. C., BROWN, A. M. and BROWNLEE, G. "Aerosporin," an antibiotic produced by *Bacillus aerosporus* Greer. *Nature*, 160: 263, 1947.
13. JAWETZ, E. and COLEMAN, A. B. Laboratory and clinical observations on aerosporin (polymyxin B). *J. Lab. & Clin. Med.*, 34: 751-760, 1949.
14. BRYER, M. S., SCHOENBACH, E. B. and BLISS, E. A. Pharmacology of polymyxin. *Ann. New York Acad. Sc.*, 51: 935-943, 1949.
15. BROWNLEE, G. and BUSHBY, S. R. M. Chemotherapy and pharmacology of aerosporin. *Lancet*, 254: 127, 1948.
16. ROSS, S., BURKE, F. C., RICE, E. C., BISCHOFF, H. and WASHINGTON, J. A. The use of aerosporin (polymyxin B) in specific and non-specific enteritis in infants and children. *M. Ann. District of Columbia*, 18: 441-503, 1949.
17. SWIFT, P. N. Treatment of pertussis with aerosporin. *Lancet*, 254: 133, 1948.
18. KAPLAN, S., FISCHER, A. E. and KOHN, J. L. Treatment of pertussis with polymyxin B. *J. Pediat.*, 35: 49-58, 1949.
19. PULASKI, E. J. and ROSENBERG, M. L. Use of polymyxin in gram-negative urinary tract infections. *J. Urol.*, (in press).
20. SCHOENBACH, E. B., BRYER, M. S. and LONG, P. H. The clinical use of polymyxin. *Ann. New York Acad. Sc.*, 51: 987-997, 1949.
21. PULASKI, E. J., CONNELL, J. F., JR. and SEELEY, S. F. Sterilization of the intestinal tract by antibiotics and supplemental agents. To be published.
22. BROWNLEE, G. Remarks on clinical results with polymyxin A and B. *Ann. New York Acad. Sc.*, 51: 998-1000, 1949.
23. KAGEN, B. M. Influenzal meningitis, recovery of a case of four weeks' duration with the use of a new drug, polymyxin B (aerosporin). *Pediatrics*. 4: 319-322, 1949.
24. LONG, P. H., SCHOENBACH, E. B., BLISS, E. A., BRYER, M. S. and CHANDLER, C. A. The experimental and clinical use of polymyxin, chloromycetin and aureomycin. *California Med.*, 70: 1-10, 1949.

Anorexia Nervosa

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric and Children's Medical Services of the Massachusetts General Hospital. These psychiatric conferences are edited by Drs. Stanley Cobb and Henry H. W. Miles. Publication is made possible by a grant from the Josiah Macy, Jr., Foundation.

DR. JOHN C. NEMIAH: D. M. (No. 628973), a twenty year old single woman, was brought to the Massachusetts General Hospital from her rooming house in a semi-intoxicated state after the ingestion of an overdose of phenobarbital. Despite a lifetime of maladjusted behavior it was not until nine months before admission that she had first come under medical surveillance. At that time following an argument with her mother, she had taken about a dozen aspirin tablets with suicidal intent. She had been persuaded to consult a psychiatrist but her visits had been irregular and four weeks later she swallowed twelve "empirin" tablets in a second attempt at suicide. After that she ran away from home. For a week she hid in a rooming house, drinking heavily, then returned to her family. She then quit college, lived by herself and managed to work for a few weeks before impulsively leaving her job. From then on she led an aimless life of job-hunting and drinking (with sporadic psychiatric interviews) until she made a third unsuccessful suicidal attempt with phenobarbital four weeks before admission. Another month of similar behavior led to the episode that brought her to the hospital.

There was no family history of psychosis. However, the mother was a fat, immature, self-pitying woman who flew into rages and endlessly scolded and argued with the patient. The father was a small man, quiet, submissive and a hard worker. The patient's only sibling, an older sister, was tense and nervous and was married to an alcoholic law student who worked as a jazz musician by night.

Her past medical history was significant

only in that at the age of five years and again at seven the patient had been knocked unconscious for brief periods, each time without known sequellae. The patient had not been a welcome addition to the family. Her mother had made futile attempts at abortion, and the patient's birth had been by cesarean section, allegedly to relieve the mother's anxieties about parturition. The mother had been unable to nurse the baby.

There had been no early childhood habit disorders other than rare enuresis. The patient's first memories reached back to the age of four years. She recalled at that time having tasted her own feces. She had immediately become panic-stricken and had been nauseated for three days. In the same year she had been caught examining a little boy's genitals and had been punished for her curiosity. At the age of five she had felt rejected by her father who once spanked her for wetting her pants; and shortly thereafter when she came into the bathroom and voided in his presence, he had become angry and chased her from the room, telling her that she was now a grown-up girl and must not do such things. After that when she wet her bed she was conscious of shame lest her father discover it.

From six to nine years of age the patient fussed with her food at meals, often throwing it out of the window rather than yield to parental demands to eat. She ran away from home several times, "played hookey" from school, developed a fiery temper and tended to withdraw from other children, preferring to play alone. At the age of ten she remembered believing that impregnation occurred by oral mixing of male and

female saliva and when shortly thereafter she learned the true facts about conception she was shocked, disgusted and upset at the thought of her parents indulging in such activities. At thirteen she first went on a diet lest she become fat like her mother. She was, at this period, a vigorous "tom boy" and had a fear of developing large breasts or looking pregnant.

Her menstrual periods which had begun when she was twelve continued with no disturbance other than mild dysmenorrhea until, at the age of fifteen, she became almost totally anorexic for several weeks and ceased menstruating. (Her periods returned after several months but have been irregular thereafter.) She lost fifteen pounds but noticed no weakness. On the contrary there was an increase in her energy and physical activity. This constellation of symptoms ended abruptly when after being disappointed by a boy she overate one day and promptly vomited. During the next two years there were several such episodes of anorexia followed by the compulsion to overeat followed by vomiting, either spontaneous or induced by tickling her throat. This sequence of gorging and vomiting became so frequent that she referred to it as "the habit." Although ashamed of the procedure, she found that it relieved feelings of depression and disappointment. During this period she ran away from a girl's boarding school where she believed herself disliked by her classmates even though she had been elected class president.

She became aware at this time of a recurrent pattern which had affected her relations with people over many years. Shortly after forming friendships she would begin to feel that her friends were disgusted by her; she would withdraw from them and purposely behave in a way to make them dislike her. She stated her feelings as: "I would rather be hated than be an object of disgust."

When eighteen years of age the patient began college. A long period of anorexia resulted in a loss of weight to 87 pounds but the patient felt so well that she was able to

continue a very active life despite frequent parties, little sleep and increasing alcoholic intake. During her second year of college she found herself less satisfied with her friends and began to resort to large doses of benzedrine to stimulate the energy which late hours, great excess of alcohol and rare marijuana smoking tended to dissipate. "The habit", became a prominent symptom, frequently occurring as often as several times a day. She began to eat classes regularly, worried a good deal whether she had had sexual intercourse while drunk and became increasingly discouraged with her life and her behavior. In this wise she continued until the suicidal attempts that preceded hospitalization.

Physical examination revealed the patient to be a small, childish looking girl who was quite thin but not emaciated. No abnormalities were found upon general physical and neurologic examinations.

Laboratory data were as follows: Urinalysis, complete blood count, chest x-ray and skull x-rays were all normal. The blood Hinton test was negative. B.M.R. was minus 11. The electroencephalogram revealed a focus of slow waves in the right occipital region and when repeated later there were slow waves in the left frontal and left occipital areas. The records were considered abnormal but contained no specific diagnostic features.

In the ward she has been at all times cooperative with the staff and has complied with the hospital rules. There have been rapid alternations of mood: within an hour or a day she may swing from a state of tearful depression to alertness and activity, at times being overenthusiastic and almost abnormally cheerful. Her compulsive stuffing of food and vomiting ("the habit") has continued, especially when she has been depressed.

In the seven weeks since admission the patient has produced an abundance of memories and associations so that the material has of necessity been very much condensed in the presentation. She has reported numerous dreams, one of which

will be mentioned because it so clearly reveals an unconscious fantasy. In the dream the patient was explaining sex to her sister and drew a diagram to illustrate. Within the outline of a human body, she drew "an ovary" (in the region occupied by the stomach) connected above to the esophagus and below to the intestines. A long penis was drawn, hanging from the part of the "ovary" adjacent to the pyloric valve. Inside the "ovary" she sketched a curled-up fetus. In explaining the dream she said that the penis discharged urine with sperm which then crept through the wall of the "ovary" in its lower portion. She corrected herself, saying: "No, it was the *upper* portion." She then said she didn't know why it seemed more natural that the sperm should enter through the upper part. Finally spontaneously she burst out: "You want me to say that the sperm went down through the esophagus."

At presentation of the patient before the group she appeared somewhat tense and was less communicative than usual although poised. When asked how she felt she replied: "A bit cautious."

DISCUSSION

DR. STANLEY COBB: This is a rather abnormal looking electroencephalogram. If she had had numerous fainting attacks or anything related to seizures, we would say the electroencephalogram was significant. It is just as abnormal as those of a lot of epileptics between attacks.

A Rorschach test would be of interest. I was interested in this case because it is said that patients with anorexia nervosa have fantasies of oral impregnation. This she has had, but I wanted to learn if suggestions of this idea by a psychiatrist could be completely ruled out. Dr. Nemiah has been careful about that and is sure that the material showed up spontaneously. So here we have evidence that seems authentic. She has said it in her own words.

For this patient a weight of 83 pounds is not very low. She is very small. She has not

reached the extremes of emaciation that some of these patients do. She has had amenorrhea in the past but recently has menstruated. The amenorrhea is usually secondary to the starvation but not always. There are some cases in which it begins before marked weight loss.

DR. JACOB E. FINESINGER: Should one be concerned with the differential diagnosis between Simmonds' disease and anorexia nervosa?

DR. COBB: At present this patient shows no endocrine disturbance. There is a history of amenorrhea. One can almost rule out pituitary disease by the history. Simmond's disease is more progressive, not so much up and down. The history is remarkably interesting, not entirely typical of anorexia nervosa; there are so many extraneous things such as several suicidal attempts, short periods of depression, alcohol which she has used rather excessively and benzedrine. I do not remember another such patient who has used alcohol and benzedrine; they often have a great drive on their starvation sprees and need no stimulant.

DR. FINESINGER: Do you remember another patient with anorexia nervosa who attempted suicide?

DR. COBB: I do not remember one who used drugs to do so. You can look on the whole episode as a suicidal attempt. I do not remember a history that showed such manic-depressive trends.

DR. HENRY H. W. MILES: Is it usual for these patients to show alternating periods of overeating and fasting?

DR. COBB: About 30 per cent of those we have observed have had starvation periods alternating with overeating periods, usually longer than those of this girl. With her, everything is short and episodic. In ordinary cases of anorexia nervosa they starve for months or years and then in the next year will overeat and go up in weight.

DR. VERNON WILLIAMS: Did she tell you why she wanted to do away with herself?

DR. NEMIAH: Her main reason is that she considers herself a "fake," she is no good, there is no point in going on with living.

She is disgusted after an episode of over-eating. She had not recognized the starvation as abnormal.

DR. COBB: It is of interest that she uses the word *disgust* which means "bad taste." At the age of ten she had the fantasy about oral impregnation. She wondered about saliva and semen. This is not rare in adolescent girls. Then in the first episode when she stopped eating, it was evidently with the idea that she did not want to be fat and sexy and would rather be like a boy.

DR. NEMIAH: She wanted to avoid secondary sex characteristics and reduce her abdomen which looked pregnant. She did not want to become fat. Her bust and hips were too big. She emphasized that she always used the word "bust" instead of "breast." The latter word she hated.

DR. LUCIE JESSNER: This is a most interesting history and I am surprised how quickly this deep material came out. I believe that the oral material is the main thing. The motto of her life, perhaps the motivation of suicide is: "I would rather be hated than disgusting." She becomes disgusted with herself, hates herself, then wishes to kill herself. It is interesting that both parents have some oral problems, too. The mother eats so much candy and gets so fat. The patient never wanted to identify with her mother who had rejected her. Her father drinks alcohol and is the one person to whom she turned, by whom she felt accepted. Rejection by him in the bathroom scene broke the one good relationship and the motif of disgust entered. She had to do a disgusting thing—had to wet the bed—after being spanked for wetting her pants. She was trying to test her parents to discover if she could be loved even though disgusting. She attempted to deny disgust by eating snow with dog feces to prove to herself that one should not be disgusted.

It seems that she gave up hope of being loved by mother or father. She tried to identify with father, tried to be a boy. Later she took to alcohol as he had done. When her feminine development became manifest it was disgusting to her. She attempted to

deny the female role. The whole eating problem is associated with denial of femininity. It seems as if, to her, eating means becoming a pregnant woman. The stomach takes the place of the ovary. Food should not get in. While she craves it, she wants to vomit it. With her, eating seems to be confused with impregnation.

I would not dare say too much about the treatment. Relationship to Dr. Nemiah, being accepted by a male person, must mean a great deal to her. She really gives him a great deal of fantasy material. That will be the mainstay of therapy;—work through with her the fantasies, how eating means impregnation. Help her realize that fantasy is not reality. One might be able to convince her of her feminine role in life which she fears.

DR. LEMOYNE WHITE: I think that this patient, in common with patients who are infantile, tends to act out her feelings and be unconscious of them. She has had more difficulty in handling her hostile feelings toward Dr. Nemiah than has been apparent today in the presentation. She is having a difficult time making a relationship, and he will have to go through a lot of discouraging behavior on her part.

DR. FINESINGER: I think she differs from typical anorexia nervosa. Her episodes of starving fluctuate more rapidly. She reacts more rapidly to symbols than does a typical anorexia nervosa. Pills have some significance. She tries to handle the problem of rejection in ways that do not succeed. She is very ambivalent and that makes it difficult for her. I have the impression that Dr. Nemiah is doing well with her. She would not have told him all this unless he had a good start with her.

What are the best areas to approach? Would it be wise to go for suicidal situations? When she tries to kill herself, it seems that she is saying symbolically: "I have tried to identify with you, but you have rejected me. You'll be sorry when I'm dead." The function of the suicidal attempt is to stir up guilt in the other person, with the idea: "You'll be sorry when I've killed

myself." That is not unusual in children and immature people.

I believe that it would be profitable to focus the interviews back to her suicidal attempts. Ventilation of these experiences might lead into the problem of rejection. This case is more like hysteria than anorexia nervosa; her prognosis is better than that of a patient with typical anorexia. It would be worth while continuing psychotherapy with her.

DR. COBB: Have you seen her mother?

DR. NEMIAH: She is a short, fat, dumpy woman. She was very excitable after the patient had taken pills. She gets into temper tantrums, yells and screams. She has taken a horsewhip to the patient several times.

DR. COBB: That fits in with other histories in anorexia nervosa. The mother drives them one way or another. Some have had their first serious attack at eighteen or nineteen when the mother began to urge them to marry and had picked out a man.

This patient is not satisfied with the starvation; she has to try suicide but the suicidal attempts are not very realistic.

DR. FINESINGER: The patient probably knows that aspirin is not going to kill her. If this is so, the pills or the act of ingestion must have some symbolic meaning. The emphasis on symbolism and the "suicidal" attempts suggest hysteria as the most probable diagnosis.

DR. COBB: Many of these patients have been handed from hospital to hospital. They are labelled schizophrenia in one clinic and hysteria in the next. They go around the circle again. I have no doubt but they look like hysteria and schizophrenia. In the last seventeen cases we have had of undoubted anorexia nervosa there were four who succeeded in killing themselves. That is a fairly high rate of mortality. Six are married and over the anorexia nervosa and have families. The other seven make their hospital rounds still.

They all have remissions. A number have them over a year or two or three. Usually the sequence is a starvation episode then a remission of a few months or a year.

They have four or five episodes and then either get over it or die. In this case the interesting aspect is that anorexia was not the main feature when she arrived, but the essence of the syndrome was learned through the interviews.

DR. FRANCES J. BONNER: I was impressed by the number of features of this case which are similar to those we have seen in many hysterias, particularly those which we have described as being very severe or very infantile. In that group one can find most of the features of this case, including oral pregnancy fantasies, ovaries in the stomach, etc.

DR. COBB: I may have exaggerated the specificity of this syndrome. Perhaps I ought to admit more of an intergradation with schizophrenia and hysteria. Anorexia nervosa was described as a syndrome by Gull in 1874 who wrote it up very well. As much as any syndrome in psychiatry I think it deserves a name.

DR. PAUL D. MACLEAN: How much significance do you give the depression?

DR. COBB: It is unusual. When these patients are starving and at their lowest some of them show a drive of energy. They are not manic in their stream of talk but show great motor activity. Others are depressed. This girl is the first one in whom I really considered manic-depressive psychosis.

Let us go ahead with her another month in the way we have. If we do not make headway, we will have to think of what next. How much psychoanalysis would help I do not know. She would be an interesting case for a control analysis.

FURTHER TREATMENT

Interviews were continued in the same manner. The patient was allowed to talk freely and spontaneously with a certain amount of "focussing" of the discussions around the suicidal attempts. These seemed to relate to a life-long pattern of behavior, i.e., when the patient developed strong positive feelings toward people (in her words, when she "got too close to people")

she would be impelled to break away. There would then be depression and the wish to die. No disturbing interpretations were made to her and the unconscious symbolism of the oral fantasies was not explained.

In the nine months since discharge the patient has not done well. Most of her symptoms have continued and she has made two more "suicidal" attempts. She has obtained and quit several jobs and joined Alcoholics Anonymous in an attempt to control her drinking. After a period of initial enthusiasm in which she immersed herself zealously in their activities, her interest waned. She quit A. A., discontinued psychotherapy and returned to live with her family. An indirect report from a member of her family indicates that her impulsiveness, mood swings and drinking are essentially as they were prior to treatment.

SUMMARY

This case of anorexia nervosa illustrates interesting psychodynamic mechanisms occurring in a girl whose symptoms also included alcoholism, tendencies toward drug addiction and rapid mood swings.

Typically, anorexia nervosa is characterized by periods of starvation, emaciation, amenorrhea and gastrointestinal discomfort. No primary metabolic or endocrine dysfunction has been established and in recent years there has been an increasing recognition of the importance of psychogenic factors. Some patients have disgust

for food although literally starving. This has been found in some cases to be associated with fantasies of oral impregnation. The act of eating or the state of being fat therefore take on a profoundly disturbing symbolic significance.¹

In many other cases no such fantasies are discovered. The patients may have no loss of appetite. They may stop eating in spite of great hunger, or they may eat and then vomit. The psychologic background may be expressed as merely a desire to remain slim and boyish. Sex may consciously enter the psychologic picture merely as an expression of the feeling that to be fat is to be voluptuous.²

In the staff discussion of this case the general characteristics of the syndrome were reviewed as well as interpretations of the patient's specific symptoms and life problems. In the treatment of such a patient hospitalization and persuasion to eat an adequate diet will often result in a remission, but this is not a cure. The illness is a serious one with a relatively high mortality rate; and unless the patient can be helped by means of psychotherapy to achieve a more adequate solution of her conflicts, the periods of starvation will probably continue, not infrequently accompanied by such serious neurotic symptoms as to necessitate commitment to a mental hospital.

¹ WALLER, J. V., KAUFMAN, M. R. and DEUTSCH, F. Anorexia nervosa: a psychosomatic entity. *Psychosom. Med.*, 2: 3, 1940.

² DuBOIS, F. S. Compulsion neurosis with cachexia (anorexia nervosa). *Am. J. Psychiat.*, 106: 107, 1949.

Clinico-pathologic Conference

Weakness, Weight Loss and Prostration*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. S., (B.H. No. 31793), was a white, married woman, forty-three years of age, who entered the Barnes Hospital for the first time on October 17, 1931, complaining of swelling of the neck, nervousness, shortness of breath and loss of weight. The family and past histories were non-contributory. Twenty years before entry during her first pregnancy the patient noted enlargement of the right side of the neck which apparently did not increase in size. Fifteen years later during her second pregnancy she became nervous, irritable and emotionally unstable and continued to be so to a varying degree during the years which preceded her first admission. Six months prior to coming to the hospital she developed shortness of breath and palpitation on exertion, and at the same time noted that she felt warm and perspired easily. Although her appetite was excellent, she had lost 30 pounds in weight. When she consulted her physician fifteen days before entry, he noted a tremor, enlargement of the thyroid gland with a bruit and thrill but no lid lag. Her blood pressure was elevated. She was given Lugol's solution by mouth and was referred to the hospital for thyroidectomy.

Physical examination at the time of entry revealed a temperature of 37°C., pulse 100, respirations 20 and blood pressure 170/65. The patient appeared restless. Her hands were moist, the skin warm and her face flushed. There was evidence of weight loss. Neither exophthalmos nor lid lag was described but there was a tremor of the

tongue, lips and fingers. Examination of the upper respiratory tract was negative. The thyroid gland was moderately enlarged, particularly on the right, but no thrill or bruit could be detected. The lungs were clear to percussion and auscultation. The heart was hyperactive. The maximal apical impulse was in the fifth interspace 10½ cm. from the midline. The rhythm was regular. A systolic murmur could be heard along the left sternal border. The peripheral pulses were bounding. The remainder of the physical examination was not remarkable.

The laboratory findings were as follows: Blood count: red cells, 4,260,000; white cells, 6,500; hemoglobin, 14.5 Gm.; differential count: within normal limits. Urinalysis: negative. Blood Kahn test: negative. Non-protein nitrogen: 27 mg. per cent; blood sugar, 117 mg. per cent, basal metabolic rate, +42. Electrocardiogram: low Q waves in Lead III.

Since the patient's condition had improved quite markedly during the fifteen days she took Lugol's solution before coming to the hospital, a subtotal thyroidectomy was performed shortly after hospital entry. The thyroid was twice normal size and both lobes were diffusely enlarged. No adenomas were present. Microscopic sections revealed changes characteristic of a diffuse toxic goiter. The patient's postoperative course was uneventful. She was discharged on November 7, 1931, and advised to continue iodine therapy.

For most of the sixteen years between her first and second admissions, the patient

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

remained essentially well; ten months before her second entry she began to lose weight and at the end of six months had lost about 30 pounds. She was seen by her physician who told her that she had "mild hypertension," but the rest of the physical findings apparently were normal. A gastrointestinal series was said to have been negative; blood counts, an electrocardiogram, and the basal metabolic rate were also within normal limits. The patient, however, continued to lose weight; her appetite failed and she vomited occasionally. One week before admission weakness became so pronounced that she had to remain in bed most of the time. Her appetite then completely disappeared and she was able to take only small amounts of liquid. She slept most of the time and on the day prior to entry was almost totally unresponsive and incoherent, being unable to recognize her surroundings or acquaintances. During the week before entry she vomited three or four times. She was admitted to the hospital on May 10, 1947.

Physical examination at that time revealed a temperature of 36°C., pulse 94, respirations 14 and blood pressure 100/70. The patient was lethargic, incoherent and prostrated. When spoken to, she slowly turned her eyes in the direction of her questioner. The skin was inelastic and dry. There was marked evidence of weight loss. No abnormal pigmentation was seen. The pupils were equal and reacted to light and accommodation; the left pupil, however, was somewhat irregular. There was moderate nicking of the retinal vessels at the arteriovenous crossings and the left disc was not quite as well outlined as the right. No hemorrhages or exudates were seen. Examination of the upper respiratory tract was not remarkable. The tongue was dry and the mouth was edentulous. Examination of the neck was negative. The lungs were clear. The heart was not enlarged; the rhythm was regular and there were no murmurs but the sounds were rather muffled. The abdomen was soft but no organs or masses were felt. The legs were

held rather rigidly and the fingers were flexed in a position which suggested mild carpospasm. The knee jerks, ankle jerks and abdominal reflexes could not be elicited. A suggestive Babinski sign was present on the right and a more definite one on the left.

The laboratory findings were as follows: Blood count: red cells, 4,500,000; hemoglobin, 12.8 Gm.; white cells, 3,000; differential count: eosinophiles, 2 per cent; stab forms, 5 per cent; segmented forms, 54 per cent; lymphocytes, 36 per cent; monocytes, 3 per cent. Urinalysis: albumin, 1+; sugar, negative; acetone, trace; sediment, negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 21 mg. per cent; blood sugar, 87 mg. per cent; CO₂ combining power, 15.3 mEq./L; chlorides, 73 mEq./L; total protein, 4.4 Gm. per cent; albumin, 2.9 Gm. per cent; globulin, 1.5 Gm. per cent. X-ray films of the skull were indeterminate. An electrocardiogram showed a P-R interval of .24 seconds.

The patient was given fluids parenterally and took some water by mouth. Early in the morning of the second day she complained of discomfort in the suprapubic region and on catheterization, 1,200 cc. of urine were withdrawn. At that time her blood pressure had fallen to 60/45. The patient was given an infusion of plasma to which adrenocortical extract was added. She also received 2,000 cc. of 5 per cent glucose in saline parenterally and 20 mg. of desoxycorticosterone acetate intramuscularly. Two-tenths of 1 cc. of epinephrine were given subcutaneously and following the plasma and fluids she received 25 cc. of adrenocortical extract intravenously. Oxygen therapy by nasal catheter was begun. The patient's blood pressure rose to 100/60 and her lungs remained clear. She became incontinent of urine and stools and her temperature rose to 38°C. Several hours later she vomited dark material; she continued to be extremely listless. Following additional amounts of adrenocortical extract intravenously, the patient's blood pressure rose

to 110/65. On the afternoon of the second day, however, it fell to 58/45 and the radial pulses became barely palpable. The patient was stuporous and her respirations were deep and stertorous. A lumbar puncture was performed and the spinal fluid was found to be entirely normal. A repeat white blood count showed 12,800 cells with 22 stab forms and 42 segmented forms. By 5 P.M. of the second day she was comatose. No clinical evidence of dehydration was present and re-examination revealed no pigmentation of the mucous membranes. She continued to receive intensive supportive therapy including plasma infusions, glucose, saline and adrenocortical extract. Despite these measures, however, early in the morning of May 12, 1947, she expired. Just before death her temperature was noted to be 38.8°C.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: In this very interesting case the history is rather straightforward. The patient, who had apparently been well most of her life, at the age of 43 developed rather classical thyrotoxicosis and following thyroidectomy was well for the ensuing 15 years. The illness which led to her death was of approximately ten months' duration, the patient's final episode being characterized by prostration. Dr. Wade, would you care to open the discussion?

DR. LEO J. WADE: I should like to ask several questions which were not answered in the protocol. First of all, was this patient's menstrual history normal? Second, what do we know of her emotional stability? And third, were there any changes in hair distribution?

DR. ALEXANDER: As far as is known, the patient's menstrual history was not remarkable. She was, however, known to be a very emotional individual. Her hair distribution was apparently normal. Why do you ask these questions, Dr. Wade?

DR. WADE: This patient apparently had multiple endocrine abnormalities and my questions were directed toward determining whether additional evidence of endocrine

inbalance was present. For example, it occurred to me that this patient may have had anorexia nervosa. In some respects the history suggests panhypopituitarism but the absence of menstrual difficulties and abnormalities of hair distribution are against that diagnosis. One must certainly consider Addison's disease which may give rise to a clinical picture such as was seen here. The relationship between the thyroid and the adrenal gland is indeed a complex one, and the effect of dysfunction in one may be reflected by changes in the other. I believe that this patient did not have Addison's disease; I would favor anorexia nervosa.

DR. WILLIAM H. OLMSTED: There are a number of factors in the history which are strongly against the diagnosis of Addison's disease. I do not remember a case of terminal adrenal insufficiency in which both the non-protein nitrogen and the blood sugar were normal. Further it is said that during the course of her last illness she was found to have hypertension and a normal basal metabolic rate. Both of these findings are uncommon in Addison's disease.

DR. ALEXANDER: I was informed that when this patient was seen about six months before entry, her systolic blood pressure was 180, and one month before entry and thus approximately one month before death it was said to be 130.

DR. OLMSTED: If the patient indeed had a blood pressure of 180 and, as was described in the protocol, she had evidence of retinal sclerosis, I would bring up the possibility of a cerebral vascular accident having been responsible for her terminal picture.

DR. ALEXANDER: Dr. Olmsted, would you tell us what signs and symptoms you think are essential to the diagnosis of Addison's disease? Are there any which you consider *sine qua non* for that diagnosis? Does the presence of hypertension enable one completely to exclude adrenal insufficiency?

DR. OLMSTED: It should be pointed out that when this patient entered the hospital she was semistuporous, and it is very difficult often in that situation to obtain certain relevant information. Low serum chlorides,

exhibit diffuse pigmentation or increased amounts in the body creases or the mucous membranes. Some of them exhibit black freckles or moles only.

DR. MACBRYDE: I agree with you. Some patients with proved Addison's disease have only slight increase in pigmentation which may, as you point out, take the form of the occasional black freckles. If such patients are followed, as their disease progresses pigmentation may increase markedly. We have had one case of proven Addison's disease in a redheaded man who had no abnormal pigmentation whatsoever.

DR. ALEXANDER: If we assume that this patient did have Addison's disease, I should like to ask Dr. Wade if he would tell us the current thought in regard to the etiology of this syndrome. How often is tuberculosis the cause of Addison's disease?

DR. WADE: Opinion on that question varies from one series of patients to another. In general it is thought to be responsible for a large number of cases; in some series figures up to 90 per cent are given. Perhaps Dr. Robert Moore could tell us what the pathologists' current view on this point is.

DR. ROBERT A. MOORE: In one series of 566 cases collected from the literature the incidence of tuberculosis of the adrenals was about 70 per cent.³

DR. ALEXANDER: In Dr. Thorn's large series the majority were non-tuberculous. On the other hand if one considers the collective series which Dr. Moore has just reported, one might raise the question as to whether patients with Addison's disease should be given streptomycin empirically. We are very fortunate in having Dr. Walsh McDermott of the Department of Medicine of the Cornell Medical School here today. He has had a substantial experience in the treatment of tuberculosis with streptomycin and I would like to ask him to comment on this point.

DR. WALSH McDERMOTT: We have recently seen one patient with Addison's

disease who developed a cold abscess of the psoas muscle without apparent involvement of bone. The adrenal insufficiency was controlled by the usual measures; although we did not think that we would either influence its course or that of the psoas abscess, we treated the patient with streptomycin. We employed the same regimen which we would use in the treatment of tuberculous empyema, that is, both systemic and local streptomycin. For several months the antibiotic exhibited a favorable effect on the abscess but subsequently the lesion flared up and showed no response to further streptomycin therapy. No change in the course of the Addison's disease was seen. One could have predicted that no change would be noted; since by the time the clinical syndrome of adrenal insufficiency had appeared, it is quite likely that so much adrenocortical tissue has been destroyed that even if the tuberculous lesions would respond completely little clinical improvement in the adrenal insufficiency would be obtained. It is conceivable that the course of very early Addison's disease due to tuberculosis might be favorably influenced if an agent is developed which is as effective against the tubercle bacillus as penicillin is, for example, against the hemolytic streptococcus.

DR. ALEXANDER: Dr. Fletcher, adrenocortical insufficiency may appear in endocrine disorders other than Addison's disease. Are there any differences in the chemical findings in adrenocortical insufficiency *per se* or in that seen in Simmonds' disease?

DR. PALMER H. FUTCHER: I think that crisis is much more common in Addison's disease than it would be in Simmonds' disease with mild adrenal insufficiency. I believe that this patient's course was typical of classical Addison's disease.

DR. ALEXANDER: Isn't the finding of a normal N.P.N. unusual in a patient only two days from death due to adrenal insufficiency?

DR. FUTCHER: I agree that it is most unusual; commonly it is elevated, reflecting changes in the kidneys secondary to de-

³ GUTTMAN, P. H. Addison's disease. A statistical analysis of 566 cases and a study of the pathology. *Arch. Path.*, 10: 742, 895, 1930.

have had some nephrosclerosis because there is a history of hypertension and slight eye-ground changes. Experimentally, the adrenals and many other organs as well are necessary for the maintenance of hypertension; clinically they must likewise exhibit normal function for maintenance of high or normal blood pressures.

DR. ALEXANDER: Do I infer from your last remark that you think that the adrenal medulla may be of importance in this aspect of the disease?

DR. SCHROEDER: No, I believe that the hypotension of Addison's disease reflects cortical destruction although even hypertensives, who become extremely ill and debilitated, may have normal or even low pressure without adrenal cortical atrophy.

DR. ALEXANDER: What is the explanation for the postural hypotension often seen in Addison's disease?

DR. SCHROEDER: It may be due either to reduced blood volume or to the relaxed state of the arterioles. When these patients are treated with DCA, the blood pressure rises and may reach true hypertensive levels. Dr. Perera in New York studied a number of patients with Addison's disease and found that with DCA and salt the blood pressure could be raised to rather high levels in about half of them.⁵ We have had a similar experience here.

DR. ALEXANDER: Dr. Massie, what do you think the heart will show in this case?

DR. EDWARD MASSIE: In patients with Addison's disease the heart is characteristically small; but if this patient really had had hypertension previously and some vascular disease, her heart may be normal in size or even slightly enlarged.

DR. ALEXANDER: Dr. Wood, do you have any comments to make?

DR. W. BARRY WOOD, JR.: Dr. MacBryde showed several years ago that there is danger attached to giving patients with Addison's disease large amounts of DCA without potassium, for under such circum-

stances the blood potassium may be lowered to a point where definite cardiac damage occurs. It has been shown experimentally that animals given potassium-deficient diets develop cardiac lesions. In this particular case the fact that the patient failed to respond to rather adequate treatment makes me wonder whether she did not have a very active tuberculous lesion. It seems to me that in most patients whose Addison's disease is in its first crisis, treatment of this order would produce a favorable response.

DR. ALEXANDER: Your point is well taken. Dr. Futcher, I believe you saw this patient. Would you comment on her therapy?

DR. FUTCHER: In retrospect, it is conceivable that this patient should have received even larger doses of adrenocortical extract and of fluids than she was given. However, as Dr. Robert Loeb has pointed out, there are patients with Addison's disease who may, when in crisis, not exhibit severe electrolyte and carbohydrate imbalances but who, despite adequate therapy, die in shock. There are certainly many factors which govern the response, in a given case, to treatment of Addisonian crisis.

DR. ALEXANDER: Are there any questions?

STUDENT: Was the prolonged P-R interval peculiar to Addison's disease or does it represent a potassium effect?

DR. MASSIE: The finding of delayed auriculoventricular conduction as evidenced by a P-R interval of 0.24 seconds is not uncommon in a patient who is in shock.

STUDENT: Can one postulate the reactivation of latent tuberculosis on the basis of the iodine therapy following thyroidectomy?

DR. McDERMOTT: There is insufficient evidence at the present time to answer that question. In this patient, however, the iodine had been given some fifteen years before her terminal episode and it seems most unlikely that it was of importance.

STUDENT: Was there any explanation of the neurologic findings which this patient exhibited?

DR. ALEXANDER: That is a very good question. Dr. MacBryde, are there specific neurologic lesions in Addison's disease?

⁵ PERERA, G. H., KNOWLTON, A. I., LOWELL, A. and LOEB, R. F. Effect of DOCA on the blood pressure of man. *J. A. M. A.*, 125: 1,030, 1944.

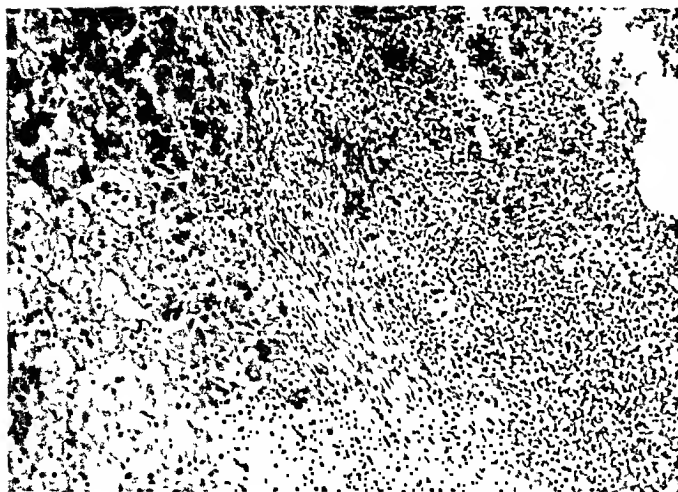


FIG. 1. Edge of tuberculous lesion of the adrenal with an adjacent small number of persistent cortical cells.

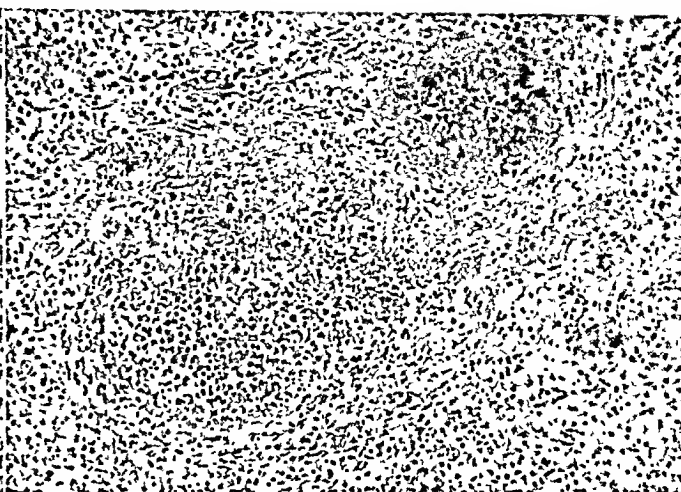


FIG. 2. Partially necrotic granulomas of tuberculosis in the adrenal gland. The stroma of the gland is extensively destroyed and replaced by fibrous tissue.

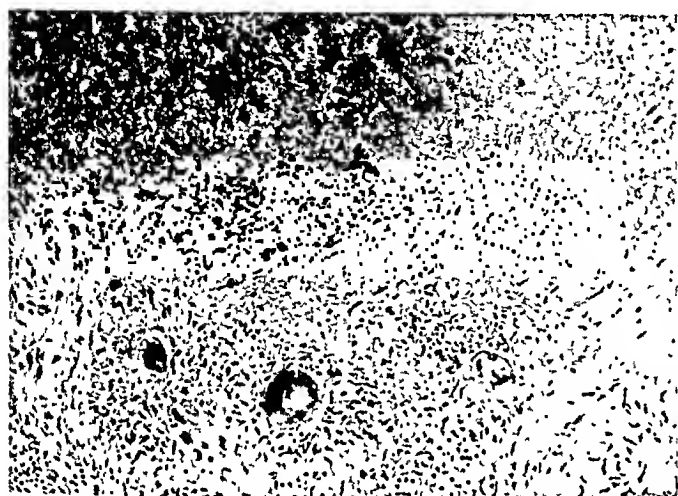


FIG. 3. Edge of a tuberculous granuloma with typical necrosis, fibrosis and giant cells. Acid-fast bacilli were identified in similar sections.



FIG. 4. Changes in the thyroid present sixteen years after subtotal thyroidectomy. The infiltration of lymphocytes and moderate storage of colloid are the most prominent features.

Hashimoto's disease in that there is a great increase of lymphoid tissue between the lobules of the thyroid. There is a moderate increase of such tissue in this section but the acini of the thyroid vary greatly in size. There is moderate storage of colloid. As lymphocytic infiltration and the formation of lymphoid tissue also occur in the thyroid gland in hyperplasia associated with hyperthyroidism, I am unable to decide whether the anatomic changes in this instance represent the residuum from old hyperthyroidism or whether they are part of Addison's disease. Certainly they are quite consistent with the changes that I have seen in Addison's disease.

In Figure 5 a section of the myocardium is seen which shows the focal fibrosis present in the sites described grossly. This change in the heart was probably the result of

coronary insufficiency inasmuch as there was a moderate to advanced degree of coronary arteriosclerosis. The other possibility is, of course, that this change might have resulted from the episode of hyperthyroidism, inasmuch as the administration of thyroid substance to animals will lead to foci of necrosis in the heart muscle. That possibility seems to me unlikely since the hyperthyroidism had occurred so many years before the patient died of Addison's disease.

The last illustration (Fig. 6) is from the liver. It is incidental to the case but demonstrated very well the appearance of the liver after a patient has received large amounts of glucose. There is a large amount of glycogen in the liver cells which gives the cytoplasm a reticulated, almost vacuolated appearance. In many places the nuclei

Coarctation of the Aorta*

E. R. HAYES, M.D. and H. M. STAUFFER, M.D.

Minneapolis, Minnesota

Philadelphia, Pennsylvania

AT this time when such remarkable strides are being made in vascular and cardiac surgery, it seems desirable to report a case of coarctation of the aorta which was found in a man aged seventy-two years. This case is particularly interesting because of the characteristic x-ray findings which are discussed in some detail.

No attempt is made to review the extensive literature on this subject; however, it is worth noting that in 200 cases collected from the literature by Abbott¹ in 1928 only two patients were over seventy years of age.

CASE REPORT

O. S., a seventy-two year old white man was admitted to the University Hospital on April 5, 1948, complaining of shortness of breath and swelling of his feet and ankles. The present illness began two years prior to admission with a severe coughing spell which came on suddenly, lasted for several hours but produced no blood or sputum. The patient had been working daily until the time of onset; there was no unusual physical exertion associated with the coughing spell. His physician was consulted and he advised bed rest for six weeks. The patient was asymptomatic at rest but when he resumed activity he noted dyspnea. There had been a gradual aggravation of dyspnea with development of orthopnea during the past two years. For the past eight months he had not been able to walk more than a block at a time and had had ankle edema.

He had been on a restricted salt intake, i.e., reduction in the amount of salt used in preparing food, but had eaten ordinary bread and butter. He had received $\frac{1}{2}$ tablet of digitalis daily for the past two years and during the eight months prior to admission had received a mercurial diuretic about once a week.

At the age of twenty-two he had been refused life insurance because of an "enlarged heart" and hypertension. He had had the usual childhood diseases and had had a subtotal gastric resection in 1943 because of a benign pyloric ulcer. At the time of surgery notching of the ribs and cardiac enlargement had been noted on x-ray examination and the diagnosis of coarctation of the aorta was suggested. He had recovered satisfactorily from his surgery and had been able to eat a relatively adequate diet. The family history and review by systems were non-contributory except as noted above.

Physical examination revealed the temperature to be 98.8°F., pulse 85, respirations 20. The pupils were equal and reacted to light and accommodation. The optic fundi showed only very minimal arteriolar sclerosis without spasm. The remainder of the examination of head and neck showed nothing abnormal. Large, tortuous, pulsating blood vessels were noted about both scapulae. The lungs revealed moist rales at both bases. Blood pressure was 180/110 in arms and 130/85 in legs. The left border of the heart was at the anterior axillary line in the fifth and sixth interspaces. No thrills were noted. There was a presystolic gallop rhythm at the apex with a soft systolic murmur. A well healed upper abdominal surgical scar was noted. Liver, spleen and kidneys were not palpable. No other abnormalities were noted. The prostate was slightly enlarged, smooth and non-tender. There was pitting edema of ankles and legs. Femoral pulsations were noted but popliteal and dorsalis pedis pulsations were absent.

Urinalysis revealed a specific gravity of 1.024; normal chemically and microscopically. Hemoglobin was 13.9 Gm.; white blood cells 10,200 with 63 per cent neutrophils; blood urea nitrogen 20 mg. per 100 cc.; serum albumin 4.0 Gm. and serum globulin 2.2 Gm. per 100 cc.; the Kline test was negative; venous pressure was 12.7 cm. of citrate in arms; vital capacity 2.8 L. (63 per cent of expected normal). An electro-

* From the Departments of Medicine and Radiology, University of Minnesota, Minneapolis, Minn.



FIG. 1. Frontal view of chest July 19, 1943. Upper arrow: dilated proximal portion of left subclavian artery. Lower arrows: left border of descending aorta. Note left ventricular enlargement of heart and marked notching of inferior surfaces of ribs.

cardiogram showed frequent ventricular extrasystoles and a left bundle branch block, a finding which had been present in 1943.

An x-ray (Fig. 1) taken on July 19, 1943, showed moderate cardiac enlargement with prominence of the left lower pole of the silhouette indicating left ventricular enlargement. The convexity of the ascending aorta was just visible along the right mediastinal contour but the prominence was insufficient to indicate significant enlargement of the ascending aorta. Along the left upper mediastinal contour there was a rounded projecting soft tissue shadow at the level where the aortic knob is normally found. The pulmonary artery shadows appeared normal. The waist-line of the heart along the left border was rather deep, and just within the cardiac contour at the level of the waist-line a second contour was visible suggesting descending aorta. This contour at its upper margin made a rather deep notch with the shadow of the projection which was presumed to represent aortic knob. Very extensive notching of the inferior aspects of the posterior portions of the lower ten ribs bilaterally could be visualized.

Fluoroscopic examination and chest films of April 6, 1948, showed marked increase in the size of the heart, again predominantly involving the left ventricle. There was at this time elevation of the soft tissue zone at the left base with



FIG. 2. Left anterior oblique view of chest April 6, 1948. Arrows point to notched shadow possibly representing narrowing at isthmus of aorta with dilated subclavian artery above. Note poor visualization of transverse portion of the aortic arch.

evidence of pleural effusion laterally, and a left lateral decubitus film demonstrated that the increased soft tissue zone at the left base represented partially loculated pleural fluid over the surface of the diaphragm. There was also a small right pleural effusion. The findings with respect to the rib notching and the upper cardiac and mediastinal contours on the left side were unchanged, the appearance still suggesting the presence of a rather prominent aortic knob. Examination in the left anterior oblique view (Fig. 2) revealed a lack of visibility of the transverse portion of the aortic arch. In this same left anterior oblique view there was a suggestion of a notched soft tissue shadow superimposed on the outline of the spine at a level corresponding rather closely with that expected for the isthmus of the aorta. This last finding was not definite and perhaps without significance although the position of the shadow suggested that it might represent the narrowed isthmus with the dilated subclavian above.

The patient was placed upon a diet which contained less than 1 Gm. of salt per day and the digitalis was increased until the patient exhibited the early symptoms of digitalis toxicity. In the course of a week the patient lost 9 pounds in weight (from 154 to 145), the rales in his lungs disappeared and dyspnea was no longer evident. The vital capacity rose to 3.41 L. (80 per cent) and venous pressure fell to 6.2 cm. of citrate.

He was completely ambulatory at the time of discharge from the hospital. He was instructed to continue on the low salt diet and to take 0.2 mg. of digitoxin daily.

COMMENT

This case seems worthy of report because of several interesting findings. In a man who had had significantly elevated blood pressure for fifty years, the changes in the vessels of the optic fundi were minimal or even "within normal limits for the patient's age," as reported by the ophthalmologist. This would seem to lend support to the theory that the vascular changes in the optic fundi as seen in essential hypertension are the product of more than the elevated blood pressure.

The fact that this patient attained an age of seventy years before he was embarrassed by a failing heart might lend support to the theory that these patients get along well until some other factor is added which leads to heart failure. In this particular case one might as well attribute the heart failure to arteriosclerotic heart disease as to coarctation. One might also theorize as to varying degrees of coarctation and believe that this represented a low degree of aortic obstruction. However, the degree of collateral circulation established would argue against such a hypothesis.

Two of the common clinical findings in coarctation of the aorta were not demonstrable in this patient, namely, the basal systolic murmur and absent femoral pulsations, yet the findings dependent upon collateral circulation were very apparent. It is possible that the low position of the

aortic arch might explain the absence of the typical basal systolic murmur.

The rib notching in this case was quite extensive and pronounced and was entirely characteristic of coarctation of the aorta. The shadow suggesting a prominent aortic knob in the presence of definite clinical and roentgen evidence of coarctation is of interest since one of the usually helpful roentgen signs is the inconspicuousness of the aortic knob. In the present case visualization of the shadow of the left border of the descending aorta well within the heart border was taken as evidence that the upper vascular projection was actually the dilated proximal portion of the left subclavian artery. Gladnikoff² has recently called attention to this finding in cases of coarctation of the aorta and also has attributed the poor visibility of the transverse portion of the aortic arch in the left oblique view to shortening and downward or medial retraction of the aortic arch.

SUMMARY

A report is made of a case of coarctation of the aorta diagnosed in a man aged seventy-two years by clinical vascular findings and x-ray evidence. This patient has lived an active life despite signs of right and left ventricular failure. He responded well to ordinary treatment for congestive failure.

REFERENCES

1. ABBOTT, MAUDE E. Coarctation of the aorta of the adult type. II. A statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of the descending arch in subjects above the age of two years. *Am. Heart J.*, 3: 392 and 574, 1928.
2. GLADNIKOFF, H. The roentgenological picture of the coarctation of aorta and its anatomical basis. *Acta radiol.*, 27: 8, 1946.

Regional Enteritis Complicated by Pylephlebitis and Multiple Liver Abscesses^{*}

FREDERIC W. TAYLOR, M.D.

Indianapolis, Indiana

THE usual and expected complications of regional enteritis are varying degrees of intestinal obstruction, local abscesses, perforation, fistulas and frequent bowel dysfunction with its attendant inanition and anemia. Recently a patient with this disease was studied at the University Hospitals. She died one month following operation with the complications of pylephlebitis and liver abscesses. The writer has never observed this complication and has been unable to find any such reports in the literature. A brief recording of the salient features of this case therefore seems warranted.

On reflection it seems strange indeed that pylephlebitis and liver abscesses are not frequently a terminal event in patients succumbing to regional enteritis. Certainly the stage is all set for such a complication, namely, a diseased bowel wall which has been invaded to the point of perforation by all manner of intestinal bacteria, a thickened inflamed mesentery which on occasion contains actual abscesses and general debility predisposing to any overwhelming infection.

This unusual complication makes interesting speculation. Possibly its rarity is due to the fact that the infection is a chronic one in which the body has ample opportunity to throw up local barriers as well as to produce a certain amount of systemic immunity. Whatever the reason, it is not the purpose of this communication to attempt an answer.

CASE REPORT

F. S. (XL 80925) was a white American woman of thirty-seven who was first admitted

to the University Hospitals in July, 1944. Her complaint was diarrhea of nine months' duration, epigastric cramps and nervousness. On this admission there were no positive findings except for a draining perirectal abscess. Laboratory findings were within normal range and no significant organisms were identified in stool cultures.

The second admission was in July, 1945, because of diarrhea, abdominal cramps, blood in the stool and a 40 pound weight loss since the onset of illness. Again findings were negative except for a low serum protein (5 Gm. per cent), a rectal fistula and occasional blood in the stool. X-ray study of the chest, esophagus, stomach, duodenum, terminal ileum and colon were negative. The patient improved on symptomatic care and was allowed to go home only to be admitted a third time one month later for excision of the rectal fistula. Pathologic study of this revealed only chronically inflamed granulation tissue. A second stage of the fistula operation was done on the fourth admission in November, 1945.

In December, 1946, the patient was admitted for the fifth time, still complaining of gas pains, diarrhea and occasional vomiting. Laboratory studies again were negative except for a moderate anemia. Further x-ray studies were made and these demonstrated a terminal ulcerative ileitis and probably ulcerative colitis. Attempts were made to improve the patient's physical condition by means of diet and transfusions. This was partially successful. Sulfasuxidine was started one week prior to contemplated surgery. Complete intestinal obstruction was never a threat in this woman although at times she became moderately distended.

On January 31, 1947, the abdomen was explored through a right lower rectus incision. The terminal 2 feet of ileum presented the typical picture of the acute phase of regional

^{*} From the Department of Surgery, Indiana University School of Medicine, Indianapolis, Ind.

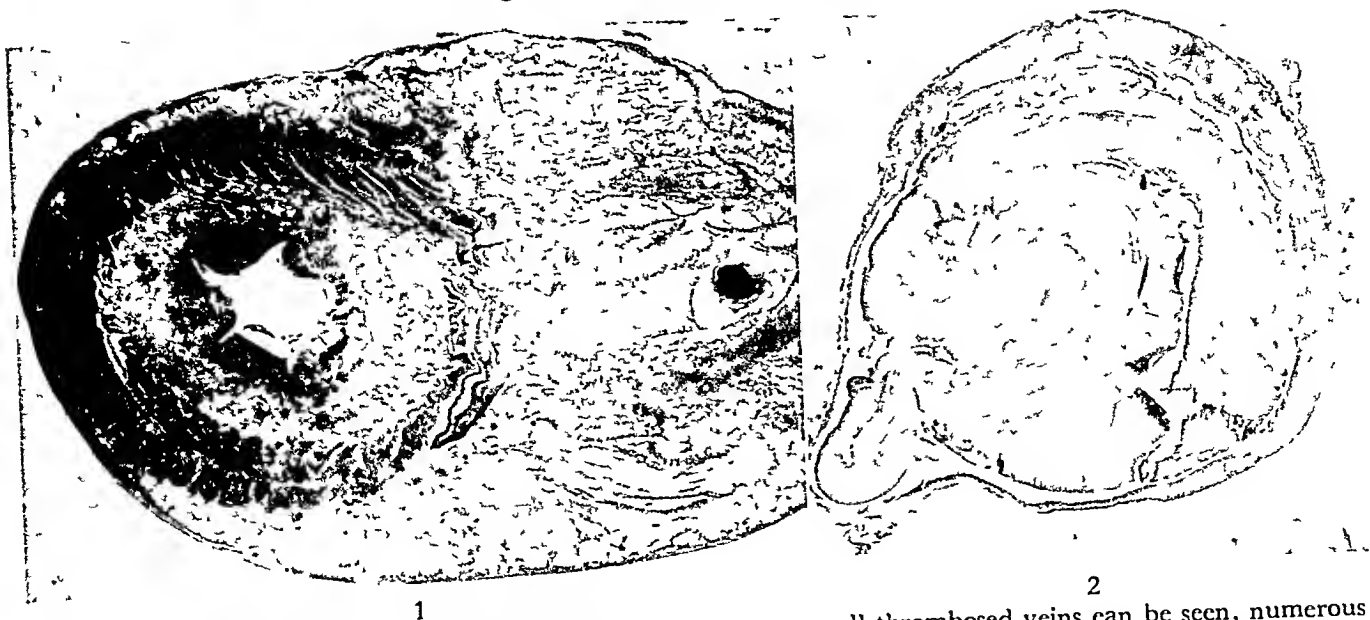


FIG. 1. Fibrosis and edema of terminal ileum and its mesentery; small thrombosed veins can be seen, numerous minute abscesses were found toward the base of the mesentery (not shown in cut). The dark group of cells to the right is hyperplastic lymphoid tissue.

FIG. 2. Portal vein completely blocked with thrombus. In the vein wall there are areas of inflammatory cell infiltration and actual suppuration.

enteritis. The gut wall was greatly thickened by a brawny edema. The rope-like portion of the bowel seemed to have practically no lumen. Its supporting mesentery was very thick, edematous and shortened. The disease stopped abruptly at the cecum and no abnormalities were noted in the ascending or transverse colon. Proximally the disease gradually decreased in intensity until the ileum appeared normal at a distance of 3 feet from the cecum. At this point the ileum was joined to the transverse colon by a simple side-to-side anastomosis, giving a $1\frac{1}{2}$ inch stoma. This was done in an anti-peristaltic direction and without dividing the distal ileum to exclude it from the circuit. Because of the patient's rather critical condition no thought was given to the possibility of a resection of the diseased gut. A lymph node removed from the mesentery of the ileum demonstrated only hyperplasia and chronic inflammation.

The postoperative course was exceptionally smooth with considerable improvement in abdominal pain and discomfort. Moderate diarrhea continued. The patient showed steady progress so that she was discharged on the twentieth postoperative day (February 20, 1947), in fair physical condition.

Six days later this patient returned complaining of vomiting and recurrence of severe diarrhea. She appeared quite ill, with a temperature of 102°F . The white blood count was 17,500 with 91 per cent polymorphonuclears; the urine was loaded with pus cells. There was

slight diffuse abdominal tenderness and distention. Lacking a definite diagnosis the patient was treated symptomatically with transfusions and intravenous fluids as indicated by blood findings. Her course was progressively downhill. She became comatose on the second day after admission and a definite icteric tint to the skin became apparent two days later. The jaundice deepened and numerous petechial hemorrhages were noted about the neck. Penicillin and sulfadiazine were given empirically with clearing of the urinary tract infection and lowering of the temperature to 99° to 100°F . The patient, however, became more comatose, dyspneic and jaundiced.

She died March 6, 1947, with an elevated total non-protein nitrogen, dependent edema and edema of lungs with pleural effusion. Death occurred thirty-four days after operation and fourteen days after she was thought to have made a satisfactory postoperative convalescence and was discharged from the hospital.

At autopsy (L2094) the condensed, pertinent findings were as follows: The abdomen contained approximately 1,500 cc. of clear bile-stained fluid. The ileotransverse colostomy was well healed with an ample stoma. Fibrosis and edema of the terminal ileum showed no change over that seen at operation. (Fig. 1.) Microscopically, numerous abscesses were demonstrated in the thickened mesentery of the ileum. Also noted were mesenteric veins containing thrombi. These thrombi could be traced upward

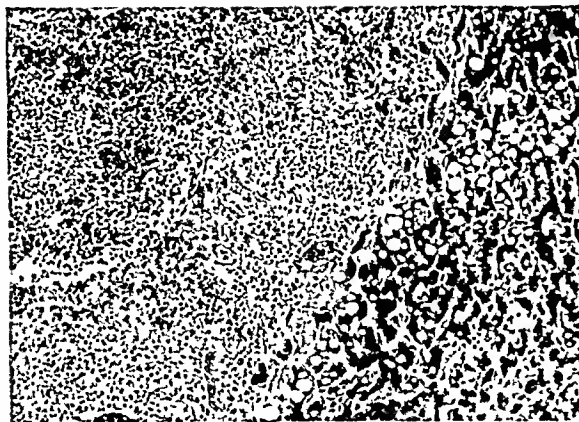


FIG. 3. Liver abscess; pus is surrounded by loose granulation tissue. Degenerative changes in the liver cells on the right are representative of those found throughout this organ.

through the superior mesenteric vein into the portal vein. Here microscopic sections demonstrated a suppurative pylephlebitis. (Fig. 2.)

The liver was yellowish brown and weighed 2,150 Gm. The cut section demonstrated many small abscesses containing a watery, gray pus. (Fig. 3.) From one or more of these hepatic abscesses pus had burrowed inside the falciform ligament, down to the anterior abdominal wall. Culture of the pus revealed a variety of organisms. (*E. coli*, non-hemolytic streptococcus, diphtheroids). These, of course, were secondary invaders forming an ascending infection from the gut to the liver. Ulcerations were present in the mucosa of the ileum. Undoubtedly the bacteria gained access to the venous channels by this route. Why the tissue invasion should have occurred in this particular manner was not explained by the postmortem examination.

The lungs demonstrated a rather extensive

terminal hypostatic bronchopneumonia. The kidneys were normal except for mild tubular degeneration. Other organs including the brain were not remarkable.

SUMMARY

A case of regional enteritis ending in pylephlebitis and multiple liver abscesses is here briefly recorded.

The writer has never seen such a complication and has been unable to find the record of a similar case. It is difficult to understand why this termination does not occur frequently in view of the lesion site and its potentialities. It is suggested that one reason for this rarity may be that the disease is fundamentally a chronic one allowing local tissue barriers as well as systemic immunity to play an important rôle.

Just when the pylephlebitis and the liver abscesses appeared in this case cannot be accurately determined from the patient's course or from the pathologic sections. It seems possible that the operative trauma was sufficient to initiate the terminal event. Since abscesses were demonstrated in the mesentery at the postmortem examination, it seems possible that these may have broken through their natural confines during the final operation, giving rise to liver abscesses. The liver abscesses on tissue section appeared to be at least several weeks old. The thrombosis of the portal vein, of course, was a terminal episode.

Hemophilia in Twins*

ARMAND J. QUICK, M.D. and JAMES P. CONWAY, M.D.

Milwaukee, Wisconsin

THE occurrence of hemophilia in twins is of special genetic interest. The appearance of the disease in one or both twins has been observed by various investigators who have gathered statistics on hemophilic families. Skold¹ in his study of sixty affected families in Sweden found four sets of twins in two of which the disease occurred in both boys. The author does not state whether these were identical (enzygotic) or fraternal (dizygotic). In a third set the boy was a bleeder while his sister was normal, but the potentiality of being a carrier remained undetermined. The fourth twins were girls both of whom were carriers since each had hemophilic offsprings. Again no mention is made whether they were enzygotic. Birch² in her series of seventy-five hemophilic families found three sets of twins. In one the boy was a bleeder and the sister normal, with the possibility of being a carrier. In another set one boy was normal while the twin brother was a severe bleeder who died of internal hemorrhage in early childhood. The third twins in the series were identical or enzygotic. Both had the same blood grouping and ran similar clinical courses.

It is logical to expect that in identical twins both should inherit the defect. The following case history is therefore not only interesting but also mystifying.

CASE REPORT

A normal mother with a negative family history of bleeding gave birth to twins, D. S. and T. S., March 31, 1942. The two boys were very similar in appearance and the mother remembers being told that there was only one placenta. Unfortunately this was not recorded on the hospital chart. Both boys were circumcised when a week old. T. S. had no abnormal

bleeding and left the hospital with his mother two days later. D. S. had severe bleeding following the operation and required a transfusion of 75 cc. of fresh blood before the hemorrhage was controlled. The coagulation time (procedure not specified) was two and one-half minutes.

Up to the age of three, D. S. had no serious hemorrhages, but it was observed that he bruised easily and developed marked swelling from trivial bumps. His brother (T. S.) at no time showed any bleeding tendency. When he was three years old, D. S. was studied by Dr. Frederick Madison and one of us (A. J. Q.) on March, 1945. The following findings were obtained:

Red blood cells. .	4,160,000	Clotting time of recalcified plasma (3)
White blood cells.	6,800	After low centrifugation—210 sec.
Hemoglobin.....	12 Gm.	After high centrifugation—225 sec.
Platelets.....	112,000	Prothrombin (100%) 12 sec.
Bleeding time. . .	3 min.	Ascorbic acid—2 mg. per 100 cc. of blood
Coagulation time (Lee-White)....	5 min.	Clot retraction—within 1 hr.

These results were inconclusive and did not permit a definite diagnosis of hemophilia; but two months later when a definite hemorrhagic episode occurred with bleeding into his groin and left thigh, positive findings were obtained:

Coagulation time (Lee-White).....	10½ min
Coagulation time of recalcified plasma	
After low centrifugation.....	180 sec.
After high centrifugation.....	360 sec.
Prothrombin (100%).....	12 sec.

From then on his clinical course has been typical of hemophilia. At one time he bled profusely from a small cut on his tongue. At another time he had a hemorrhage into his right knee. He has never had nose bleeds, an observation

* From the Department of Biochemistry, Marquette University School of Medicine and Milwaukee Children's Hospital, Milwaukee, Wis. This work was supported by a grant from the United States Public Health Service.

which is not surprising since many hemophilics never have epistaxis.

His bleeding episodes appear to be cyclic and often are initiated by prodromal manifestations. This is particularly well illustrated by the following incident: For no accountable reason he suddenly began to feel listless and complained of being unusually tired. Following this he lost his appetite and two days later began vomiting and complained of pain in the abdomen with localization over McBurney's point. This necessitated making a diagnosis of acute appendicitis although the possibility of abdominal hemorrhage was recognized. The decision to operate was made. He was given 300 cc. of lyophilized plasma intravenously. The transfusion was started an hour before the operation and completed during the operation. The appendix was found normal but there was a retroperitoneal hemorrhage behind the cecum. The appendix was removed and special care was taken to tie off all bleeders. No unusual bleeding was encountered. The administration of plasma definitely improved the hemostatic property of his blood as shown by the prothrombin consumption test.^{4,*} The time was eleven seconds before the transfusion and twenty-one seconds after he received the plasma. Two and one-half days after the operation it was still twenty-one seconds and the coagulation time (Lee-White) seven and one-half minutes. Twenty-four hours later, however, the prothrombin consumption time was eleven seconds and he was bleeding into his incision. He was given 250 cc. of fresh blood. The prothrombin consumption time immediately increased to twenty-five seconds, hemorrhage was controlled and he had no further bleeding.

He had another unusual bleeding episode. As the result of a cold he developed a severe cough. Apparently from strain he ruptured a small vessel in the anterior neck and bled into the mediastinum; this was verified by roentgenologic examination. He was given a transfusion of 250 cc. fresh whole blood. The prothrombin

* The prothrombin consumption test consists in allowing blood to coagulate and then determining the prothrombin remaining unconverted in the serum. The test is carried out as follows: 0.1 cc. of human oxalated plasma treated with calcium phosphate (which serves as the source of fibrinogen) is mixed with 0.1 cc. of thromboplastin and 0.1 cc. of 0.02 M calcium chloride. To this mixture, 0.1 cc. of serum is rapidly added from a pipette and the formation of a clot accurately timed. Normal blood has a prothrombin consumption time of sixteen to thirty-five seconds, whereas hemophilic plasma has a value varying from nine to twelve seconds.

consumption time before the transfusion was ten and one-half seconds and sixteen and one-half seconds after the blood was given.

While D. S. is a typical hemophiliac, his twin brother is entirely normal. There is evidence that they are identical twins. Some of the similarities are:

	D. S.	T. S.
Eyes	Hazel brown	Hazel brown
Nose and ears . .	Same shape and size (including type of ear lobe)	
Hair	Very dark brown Same type whorl and identically located	Very dark brown
Height	48½ in.	47¼ in.
Weight	48 lb.	46 lb.
Blood grouping .	A ₁ MN Rho'	A ₁ MN Rho'*
Probable genetic pattern	CDe/CDe	CDe/CDe
Mothers blood grouping—BM Rho'	(CDe/CDe)	

* We are indebted to Dr. Tibor J. Greenwalt and the Junior League Blood Center of Milwaukee for these studies.

The coagulation studies of the family were:

	D. S.	T. S.	Father	Mother
Coagulation time (Lee-White)	13½	5½	6	5 min
Coagulation time of recalcified plasma				
After high centrifugation	600	135		sec
After low centrifugation	210	105		sec
Prothrombin time	12½	12½	12½	12½ sec
Prothrombin consumption time				
After 1 hr	11	19	20	18 sec
After 4 hr	12	23	25	23 sec

After mixing 1 cc. of D. S. blood with 1 cc. of his brother's a coagulation time of six minutes resulted and the prothrombin consumption time was twenty seconds in one hour.

COMMENT

From the data presented it is clear that one twin is a typical hemophiliac whereas his brother is entirely normal. All the evidence obtainable strongly indicates that these boys are identical twins. Their blood types are exactly the same. They are very similar in appearance. (Fig. 1.) The hemophilic boy is a little taller and heavier which his mother attributes to the greater

amount of rest he receives. The color of the eyes and the shade of their hair are identical and even such details as the type and location of the whorl of their hair completely match. There is a similarity of their finger prints, but these have not been studied thoroughly. If it were not for the finding that one is a bleeder and the other normal, one would unhesitatingly classify them as enzygotic. Assuming that they are identical twins, one is at a loss to explain how one has the characteristic defect of true hemophilia while the other escaped this inborn error in the blood.

Since the family history as far as it is obtainable is negative, the simplest explanation would be to postulate a mutation in the affected twin and class him as a sporadic hemophiliac. But one must be extremely cautious in calling any case sporadic in view of the insidious heredity pattern of the disease. If it were common for this disease to originate *de novo*, one would expect an incidence in the negro approximating that of the white race. Yet it is doubtful whether true hemophilia has ever been unequivocally demonstrated in a person of pure negro ancestry. It must be emphasized that the diagnosis of hemophilia was never conclusive until the development of recent methods particularly the prothrombin consumption test, and that acquired hemophilia-like disease^{5,6} and the hereditary types of congenital hypoprothrombinemia⁷ closely resemble true hemophilia clinically, and are also characterized by a prolonged coagulation time.

In view of these considerations no attempt will be made to explain the paradoxical occurrence of hemophilia in only one of presumably identical twins. The purpose of this paper is merely to present this unusual observation, since with the accumulation of such diverse findings more light may be shed on the peculiarities of inheritance.

SUMMARY

The history, clinical and laboratory findings are presented of a hemophilic boy who is one of presumably identical twins. His brother is entirely normal.



FIG. 1. D. S., the hemophilic twin, is on the left. Due to hematomas, particularly of the forehead, and scarring about the mouth, the facial features have been somewhat changed. Consequently the similarity in appearance of D. S. and T. S. is not as striking as is often observed in identical twins.

REFERENCES

1. SKOLD, E. On hemophilia in Sweden and its treatment by blood transfusion. *Acta med. Scandinav.*, 150: 247, 1944.
2. BIRCH, C. L. Hemophilia: Clinical and Genetic Aspects. Illinois Medical and Dental Monograph, No. 4, University of Illinois, 1937.
3. QUICK, A. J. The diagnosis of hemophilia. *Am. J. M. Sc.*, 190: 469-474, 1935.
4. QUICK, A. J. Studies on the enigma of the hemostatic dysfunction of hemophilia. *Am. J. M. Sc.*, 214: 272-280, 1947.
5. MADISON, F. W. and QUICK, A. J. Hemophilia-like disease in the female. With a note on the clotting time of recalcified plasma. *Am. J. M. Sc.*, 209: 443-447, 1945.
6. QUICK, A. J. and STEFANINI, M. Activation of plasma thromboplastinogen and evidence of an inhibitor. *Proc. Soc. Exper. Biol. & Med.*, 67: 111-112, 1948.
7. QUICK, A. J. Congenital hypoprothrombinemia and pseudo-hypoprothrombinemia. *Lancet*, 2: 379, 1947.

Book Reviews

The Parathyroid Glands and Metabolic Bone Disease. Selected Studies. By Fuller Albright, M.D. and Edward C. Reifenstein, Jr., M.D. 393 pages. Baltimore, 1948. The Williams and Wilkins Company. Price \$8.00.

New publications of Fuller Albright and his associates at the Massachusetts General Hospital are always received with interest; this concise, authoritative monograph summarizes the group's major contributions to the field of calcium and phosphorus metabolism during the past two decades.

Although emphasis is given to hyperparathyroidism, osteoporosis and osteomalacia, considerable information about other diseases of bone is included. The discursive style makes pleasant reading, the numerous illustrations are well chosen and the twenty-page bibliography covers most of the relevant literature.

The chapter on physiology is short but adequate. Without embarking upon extended technical discussions, the authors review the available evidence dealing with the action of the parathyroid glands and the formation and maintenance of bone. It is evident here, as stated in the preface, that their "hypotheses . . . are subject to change without notice." Although the authors' theories of parathormone action have been modified to include a direct action on bone, the recent work of Jahan and Pitts and of Stoerk may require that further modification be made in the next edition.

A few theoretical inconsistencies appear in the monograph; attention should be called to at least one of these: The dangers of metastatic calcification in chronic renal insufficiency are emphasized in the section on "parathyroid poisoning"; some paragraphs later, however, treatment with alkali, vitamin D and a high calcium intake is recommended for the bone disease sometimes accompanying this disorder. Although the resulting increase in calcium absorption from the intestinal tract may produce "spectacular" improvement in the osteitis fibrosa generalisata, progressive renal damage would seem inescapable.

In the same chapter acidosis is held to be the cause of the bone disturbance in secondary hyperparathyroidism; the relation of acidosis occurring in renal tubular disease without nitrogen retention to the associated osteomalacia is, however, not mentioned in the discussion of this disease. There is little question that the authors' conception of the pathogenesis of the bone disorder accompanying renal tubular acidosis will require some modification as new evidence is obtained. The value of their contribution to the treatment of this disorder, however, remains undisputed.

There are few publications in the field of bone disease in which as much fundamental information is so authoritatively presented and applied to clinical problems in so brief a space as in this monograph. It will be of interest to the practicing physician as well as to the student of bone disease.

K.L.P.

Communicable Disease Control. By Gaylor W. Anderson, and Margaret G. Arnstein, M.D., 2nd ed., 450 pages. New York. The Macmillan Co. Price \$5.00.

This second edition of an introductory reference book of preventive medicine brings to the reader an up-to-date account of the available control measures in the realm of communicable diseases. As is emphasized by the authors the material is primarily concerned with community protection rather than with the handling of individual patients with infectious diseases.

The first part of the book briefly covers the regulations and responsibilities of the various local, state and federal agencies, while the remaining sections evaluate the different control measures available in specific communicable diseases.

For general public health purposes the subject is covered in great enough detail. For those wishing to pursue particular problems in greater detail the authors have included adequate references at the conclusion of each chapter.

A.R.L., JR.

AUTHOR INDEX VOLUME VII

- Andrews, Gould A., 564
- Balfour, William M., 596
- Ball, Con O. T., 356
- Barach, Joseph H., 617
- Barnes, Zerney B., Jr., 518
- Beams, A. J., 425
- Bean, William Bennett, 765
- Becker, Marvin C., 269
- Benner, William H., 553
- Billings, F. Tremaine, Jr., 356
- Bland, John H., 288
- Bloomfield, Arthur L., 437
- Blumenthal, Sunoll A., 501
- Boots, Ralph H., 741
- Brennan, Andrew J., 431
- Brod, Jan, 317
- Brown, Thomas McP., 431
- Bubis, Sylvia, 336
- Carmody, M. G., 345
- Cathcart, Richard T., 439
- Chanutin, Alfred, 297, 301
- Christian, William A., 553
- Conway, James P., 841
- Cournand, Andre, 439
- Dack, Simon, 464
- Danowski, T. S., 525
- DeNardi, J. M., 345
- Dickie, Helen A., 690
- Dock, William, 751
- Erwin, James H., 336
- Favour, Cutting B., 511
- Fazekas, Joseph, 262
- Fenn, G. K., 35
- Ferrer, M. Irene, 439
- Field, Leonard E., 464
- Findley, John W., Jr., 198
- Findley, Thomas, 70
- First, Safety R., 760
- Fischel, Edward E., 772
- Fishman, Alfred P., 15
- Flamm, Gerald W., 765
- Freis, Edward D., 647
- Gardner, Carl, 3
- Garver, Hortense Elton, 694
- Goetz, Frederick C., 274
- Goldberger, Emanuel, 756
- Goldman, Melvin L., 454
- Greisman, Harry, 310
- Grimm, Elizabeth, 690
- Grishman, Arthur, 464
- Griswold, Dwight, 686
- Grokoest, Albert W., 741
- Guest, George M., 630
- Gutman, Alexander B., 1
- Haist, R. E., 585
- Hamilton, Howard B., 56
- Harmos, O., 425
- Harvey, Rejane M., 439
- Hayes, E. R., 835
- Hellerstein, Herman K., 660
- Herring, Albert C., 686
- Horn, Henry, 464
- Houck, George H., 699
- Hyman, Abraham, 15
- Ingelfinger, Franz J., 168, 174
- Jaffe, Herbert, 702, 718
- Johnson, Balbina A., 794
- Kahn, Stanley S., 655
- Kalstone, Bernard M., 356
- Keefer, Chester S., 216
- Kirsner, Joseph B., 198
- Kneeland, Yale, Jr., 532
- Kramer, Philip, 168, 174
- Kroop, Irving G., 15
- Lasner, J., 35
- Leard, Samuel E., 647
- Leiter, H. Evans, 15
- Lepow, Harold, 310
- Levine, Samuel A., 478
- Liebow, Irving M., 660
- Lillian, Marvin, 280
- Little, J. Maxwell, 207
- Machella, Thomas E., 191
- Mann, George V., 3
- Marks, Jerome A., 180
- Master, Arthur M., 464
- McDermott, Walsh, 371
- Meleney, Frank L., 794
- Meneely, George R., 356
- Miller, T. Grier, 153
- Movitt, E. R., 145
- Nalefski, L. A., 35
- Newman, Elliot V., 490
- Palmer, Walter Lincoln, 198
- Pearsall, H. Rowland, 297, 301
- Perera, George A., 56
- Peterson, Edwin W., 274
- Phillips, Edward, 478
- Pines, Kermit L., 56
- Price, Harry J., 518
- Pullman Theodore N., 198
- Quick, Armand J., 841
- Quimby, Edith H., 731
- Ragan, Charles, 741
- Ransmeier, John C., 518
- Richards, Diekinson W., Jr., 439
- Riser, A. Bankston, 655
- Robertson, O. H., 293
- Rogers, Walter F., Jr., 702, 718
- Root, Howard F., 3
- Rose, Harry M., 532
- Rubenstein, Leo, 310
- Rubin, Samuel H., 288
- Sapadin, Albert, 765
- Schloss, Eugene M., 156
- Schmidt, Charlotte, 731
- Schroeder, Henry A., 454
- Schutz, Paul J., 553
- Schwartz, Steven O., 501
- Senter, William J., 694
- Smadel, Joseph E., 671
- Sommer, Leonard S., 511
- Spencer, James L., 356
- Spingarn, Clifford L., 269
- Sprague, Randall G., 596
- Stanley, Maleolm M., 262
- Stansly, Philip G., 807
- Stauffer, H. M., 835
- Stetten, DeWitt, Jr., 571
- Stock, Richard J., 45
- Strax, Selig, 180
- Sutker, Harold, 694
- Tagnon, Rene, 702, 718
- Taubman, Felix, 751
- Taylor, Frederic W., 838
- Tompsett, Ralph, 371
- Towery, Beverly T., 702, 718
- Van Ordstrand, H. S., 345
- Vesell, Harry, 497
- Vislocky, Katherine, 56
- Vranian, George, 431
- Waksman, Selman A., 85
- Warren, Joel, 431
- Werner, Sidney C., 731
- White, Priscilla, 609
- Wiesel, Bert H., 655
- Wilder, Russell M., 569
- Wilder, Russell M., Jr., 625
- Williams, Robert H., 702, 718
- Williams, Russell D., 137
- Winans, H. M., 150
- Woll, Fanya, 310
- Wright, Louis T., 180

SUBJECT INDEX VOLUME VII

(E.) = Editorial

Abstracts

- of papers of American Federation for Clinical Research, 126, 407
- of papers of Southern Society for Clinical Research, 241
- ACTH in rheumatoid arthritis, 741
- Addison's disease, Kendall compound E in, 56
- Adenomatosis, pulmonary, 336
- Adrenal cortex, 100
 - disorders of, and diabetes, 596
- Adrenocorticotrophic hormone (ACTH) in rheumatoid arthritis, 741
- Allergy
 - and rheumatic fever, 772
 - intestinal, intubation in, 156
- American Federation for Clinical Research, 126, 407
- Anemia, iron-deficient, and hiatus hernia, 501
- Aneurysms in pulmonary artery, 280
- Anorexia nervosa, 819
- Antibiotics, origin and nature of, 85
- Arteriosclerosis and diabetes, 617
- Aureomycin
 - for infectious diseases, 532
 - for ulcerative colitis, 180
 - in tularemia, 518
- Auricular
 - fibrillation without evidence of heart disease, 478
 - flutter, treatment of, with digitalis (E.), 437
- Azotemia, 542
 - transperitoneal lavage for, 35

Bacitracin, 794

- Ballistocardiogram, 751
- Blood pressure measurement in coarctation, 454
- Boeck's sarcoid and tuberculosis, 760
- Bone marrow, megaloblastic, in liver disease, 145
- Book reviews
 - Communicable Disease Control (Anderson and Arnstein), 844
 - Parathyroid Glands and Metabolic Bone Disease (Albright and Reifstein), 844

Carbohydrate metabolism, 571

- Cardiac
 - complications of diabetes mellitus, 660
 - failure, 207
 - and function of kidney, 490
 - elevated basal metabolic rate and psychosis, 228
- Cardiospasm and esophageal motility, 174

- Chloramphenicol in infectious diseases, 671
- Clinics on psychosomatic problems (Massachusetts General Hosp.)
 - Anorexia nervosa, 819
 - Psychogenic deafness in a disturbed boy, 221
- Clinico-pathologic conferences (Washington Univ.)
 - Cardiac failure, elevated basal metabolic rate and psychosis, 228
 - Chronic pleurisy and peritonitis, 396
 - Pneumonia, skin eruption, thrombophlebitis and azotemia, 542
 - Progressive hepatic disease, 114
 - Weakness, weight loss and prostration, 825
- Coarctation of aorta, 454, 835
- Colitis
 - ulcerative, and aureomycin, 180
 - hyperalimentation in, 191
- Columbia combined staff clinics
 - Acute diffuse glomerulonephritis, 382
 - Adrenal cortex, 100
- Coma, diabetic, 630
- Combined staff clinics (Columbia Univ.)
 - Acute diffuse glomerulonephritis, 382
 - Adrenal cortex, 100
- Coronary insufficiency due to pulmonary embolism, 464
- Cysts, pulmonary, 280

Deafness, psychogenic, 221

- Dehydration and plasma volume, 647
- Diabetes
 - and arteriosclerosis, 617
 - and cardiac complications, 660
 - and insulin mixtures, 655
 - and pregnancy, 609
 - experimental, 585
 - in general practice, 625
 - mellitus and disorders of pituitary, thyroid and adrenal cortex, 596
 - and glomerulosclerosis, 3
 - Kendall compound E in, 56
- Diabetic coma, 630
- Digitalis for auricular flutter (E.), 437
- Digoxin, effects of, upon heart and circulation, 439
- Disinfection of air with triethylene glycol vapor (E.), 293

Embolism, pulmonary, and coronary insufficiency, 464

- Endarteritis of ductus arteriosus, 280
- Endocarditis due to *Hemophilus influenzae*, 274

Enteritis, pylephlebitis and liver abscesses, 838
Epileptic equivalents and somatic symptoms, 150
Esophagus, disorders of, 168

Fibrosis, interstitial, of lungs, 425

Gastritis, chronic, 198

Glomerulonephritis, acute, diffuse, 317, 382

Glomerulosclerosis, intercapillary, in diabetes mellitus, 3

Granulomatosis, pulmonary, 345

Heart

clockwise rotation of, 756

effects of digoxin on, 439

failure, reversible, cause of, 478

Hemiplegia and myocardial infarction, 765

Hemophilia in twins, 841

Hemophilus influenzae and endocarditis, 274

Hepatic disease, progressive, 114

Hiatus hernia, diaphragmatic, 501

Hydration and shifts in fluid compartments, 647

Hyperalimentation in ulcerative colitis, 191

Hyperparathyroidism and thyrotoxicosis, 262

Hypertension

and neurohypophysis, 70

Kendall compound E in, 56

Hyperthyroidism, radioactive iodine in, 731

Infarction, myocardial, 356

Infections, systemic, penicillin for, 216

Infectious diseases and chloromycetin, 671

Insulin mixtures, 655

Intubation studies in intestinal allergy, 156

Kala-azar, 694

Kendall compound E in hypertension, 56

Kidney, function of, and metabolism in cardiac failure, 490

Kolff artificial kidney, 15

Lavage, transperitoneal, for azotemia, 35

Lipodystrophy, intestinal, 553

Liver

abscesses, enteritis and, 838

disease, bone marrow in, 145

Loeffler's syndrome with polyserositis, 690

Lungs, interstitial fibrosis of, 425

Massachusetts General Hosp. clinics on psychosomatic problems

Anorexia nervosa, 819

Psychogenic deafness in a disturbed boy, 221

Meningitis, influenzal, in adults, 269

Mononucleosis, infectious (E.), 699

Motility of human esophagus, 168

Myocardial infarction
and hemiplegia, 765
prognosis of, 356

Nephrotic syndrome and influenzal meningitis, 269

Neurohypophysis in hypertension and allied disorders, 70

Pancreatitis, chronic, 137

Panniculitis, non-suppurative, 288

Penicillin

for systemic infections, 216

therapy, complications of, 511

Peritonitis, chronic, 396

Plasma

and plasma fractions, analyses of, 297, 301

volume during hydration and dehydration, 647

Plethysmography in diagnosis of coarctation, 454

Pleurisy, chronic, 396

Pneumonia, 542

Polyarteritis nodosa, diagnosis of, 310

Polycythemia vera, radioactive phosphorus treatment of, 564

Polymyxins, 807

Polyserositis, eosinophilic, and Loeffler's syndrome, 690

Potassium, role of, in disease, 525

Pregnancy complicating diabetes, 609

Protein, precipitable, in human sera, 310

Psychosis and cardiac failure, 228

Pulmonary

adenomatosis, 336

artery aneurysms, 280

granulomatosis, 345

Pylephlebitis, enteritis and, 838

Radioactive iodine I^{131} in hyperthyroidism, 731

Radioiodotherapy, 702, 718

Rheumatic fever and allergy, 772

Rheumatoid arthritis, ACTH in, 741

Rotation of heart, clockwise, 756

Seminars on antibiotics

Aureomycin in the treatment of infectious diseases, 532

Bacitracin, 794

Chloramphenicol (chloromycetin) in the treatment of infectious diseases, 671

Dosage forms of penicillin for systemic infections, 216

Origin and nature of antibiotics, 85

Recent advances in streptomycin therapy, 371

Southern Society for Clinical Research, 241

Streptomycin therapy, advances in, 371

Tetanus after dental extraction, 686

Thrombocytopenic purpura in polycythemia vera, 564

Thrombophlebitis, 542

Thyrotoxicosis simulating hyperparathyroidism, 262

Toxoplasma infection, 431
Tricuspid stenosis, 497
Triethylene glycol vapor for disinfection of air (E.), 293
Tuberculosis, pulmonary, and Boeck's sarcoid, 760
Tularemia, aureomycin in treatment of, 518

Ulcer, peptic, vagotomy for (E.), 153
Urinary suppression, acute, 45

Vagotomy for peptic ulcer (E.), 153

Washington Univ. clinico-pathologic conferences
Cardiac failure, elevated basal metabolic rate and
psychosis, 228
Chronic pleurisy and peritonitis, 396
Pneumonia skin eruption, thrombophlebitis and
azotemia, 542
Progressive hepatic disease, 114
Weakness, weight loss and prostration, 825
Weber-Christian disease, 288
Whipple's disease, 553

